EXHIBIT 612.1

CURRICULUM VITAE

William L. Galanter, M.D., Ph.D.

PRESENT POSITION:	Assistant Professor of Clinical Medicine Clinical Assistant Professor of Pharmacy Practice Medical Director, Clinical Information Systems Medical Director, UIC Physicians Group University of Illinois College of Medicine
WORK ADDRESS:	940 S. Wood, M/C 718, Chicago, IL, 60612
E-MAIL	BillG@uic.edu
STATE LICENSE:	Illinois #036-093837-01
BOARD CERTIFICATION:	NBIM passed 12/96, recertified 12/2006

EDUCATION

B.S., Physics, with honors, University of Illinois, Urbana, 1984
M.S., Physics, University of Illinois, Urbana, 1986
Ph.D., Physiology & Biophysics, University of Illinois at Chicago, 1993
M.D., University of Illinois at Chicago, 1993
Internal Medicine Residency, University of Illinois at Chicago, 1993-96
Faculty Development Fellowship, University of Illinois at Chicago, 1998

PRIOR POSITIONS

Department of Physics, University of Illinois, Urbana;
Teaching assistant for pre-medical physics, 1983-86
Part-time lecturer for pre-medical physics, 1986
Research Assistant: 1985-86

Departments of Physiology & Biophysics and Pediatrics, University of Illinois at Chicago;
Research Assistant: 1988-91
Teaching assistant for elementary physiology, 1988-89
Part-time lecturer for elementary physiology, 1989-91

Chief Resident, University of Illinois Hospital, Department of Internal Medicine, 1996-97

Associate Program Director, UIC, Department of Medicine 2000-3
Director, UIC Ambulatory Medicine Clerkship 1998-2003
Director, UIC Medicine Clerkship, 2002-3

COMMITTEE MEMBERSHIP

Chair, University of Illinois Medical Center Clinical Decision Support Committee
Chair, University of Illinois Medical Center, Pharmacy & Therapeutics Committee

ADMINISTRATIVE RESPONSIBILITIES

Chair, University of Illinois Hospital Pharmacy & Therapeutics Committee
Medical Director, UIC Physicians Group

TEACHING RESPONSIBILITIES

Preceptor to Medical Students in Ambulatory Medicine Clerkship, 1997 to present
Preceptor to housestaff in the General Medicine Clinic, 1997 to present
Medical Student Advisor, 1997 to present

HONORS

College of Medicine, AOA Clinical Teaching Award, 2008

Department of Medicine, Teaching Excellence Award for top 10% of Faculty, 2003, 2004, 2006, 2007

Faculty Inductee into Alpha Omega Alpha honor society, 2002

New Jersey Healthcare Foundation Humanism Award, University of Illinois, College of Medicine, 2002

Honorary faculty to Hood Graduates at the UIC College of Medicine Graduation, 2000 & 2002

Attending Physician of the Year in the Department of Medicine, 2000

Raymond B. Allen "Golden Apple" Award for Excellence in Teaching, UIC, College of Medicine, 1999

PGY-III of the Year Award, University of Illinois, Department of Medicine, 1996

PGY-II of the Year Award, University of Illinois, Department of Medicine, 1995

Trainee Investigator Award, American Federation of Clinical Research (AFCR), Baltimore, 1992

Leon F. Muldovsky Scholarship for outstanding student in Physiology, University of Illinois at Chicago, 1991

National Student Research Forum, Roche Laboratories award for excellence in basic science research, First place, graduate student division, 1991

National Student Research Forum, Roche Laboratories award for excellence in basic science research, First place, graduate student division, 1990

Anderson Award for outstanding Teaching Assistant in the Department of Physics, UIUC, Urbana, 1985

PUBLICATONS

1. Schiff GD, Galanter WL, Duhig J, Lodolce AE, Koronkowski MJ and Lambert BL. . *Principles for More Conservative Prescribing*. Arch Intern Med. 2011; In Press.

2. Walton SM, Galanter WL, Rosencranz H, Meltzer D, Stafford RS, Tiryaki F, Sarne D. *A trial of inpatient indication based prescribing during computerized order entry with medications commonly used off-label*. Appl Clin Inf. 2011; 2: 94–103.

3. Yu, S. Galanter WL, Didomenico, RJ, Borkowsky S, Schiff G, Lambert B. *Consensus list of priority drug-lab linkages for an inpatient asynchronous alert program: Results of a Delphi survey*. Am J Health-Syst Pharm. 2011. Mar 1;68:407-414

4. Yudkosky, R, Galanter W, Jackson R. *Students overlook information in the electronic health Record*, Med Ed 2010; 44:132-133

5. Galanter, WL, et al. *Clinical Decision Support to Improve Venous Thromboembolism Risk Assessment, Prophylaxis and Prevention at a University Teaching Hospital*. Am J Health-Syst Pharm. 2010. Aug 1;67(15):1265-73.

6. Galanter, WL, Liu, X and Lambert, BL. *An Analysis of Computer Alerts Suggesting Oral Medication Use During Computerized Order Entry of Intravenous (IV) Medications*. Am J Health-Syst Pharm. 2010. Jul; 67, Issue 13, 1101-1105

7. Galanter, W.L., Hier, D.B., Jao, C. and Sarne, D. *Computerized physician order entry (CPOE) of medications and clinical decision support (CDS) can improve problem list compliance*. Int J Med Inform. 2010 May;79(5):332-338

8. *Formulary Leveraged Improved Prescribing: Tool for Guiding Critical Formulary Decision Making. The AMCP Format for Formulary Submissions Ver. 3.0.* J Manag Care Pharm. 2010 Jan;16(1): Supplement, Appendix G, 2010

9. Darabi, H., Galanter, W.L., Lin, J, Buy, U and Sampath, R. *Modeling and Integration of Hospital Information Systems with Petri Nets*, Proceedings of the 2009 IEEE International Conference on Service Operations, Logistics and Informatics. July 2009, 190-195.

10. Schiff GD and Galanter WL. *Promoting More Conservative Prescribing*. JAMA. 2009;301(8):865-67.

11. Jao CS, Hier DB, Galanter WL. *Using clinical decision support to maintain medication and problem lists: A pilot study to yield higher patient safety*. Proc 2008 IEEE Int'l Conf on Systems, Man and Cybernetics. *2008:739-43.*

12. Baumann, J, Didomenico, R and Galanter, W. *Mechanisms, manifestations, and management of digoxin toxicity in the modern era*. Am J Cardiovasc Drugs, 2006:6(2):77-86.

13. Galanter, W.L., Didomenico, R and Polikaitis, A. *A trial of automated decision support alerts for contraindicated medications using computerized physician order entry.* J Am Med Inform Assoc. 2005 May-Jun;12(3):269-74.

14. Galanter, W.L., Didomenico, R and Polikaitis, A. *Effectiveness of automated clinical decision support alerts for inpatient digoxin use with computerized physician order entry.* J Am Med Inform Assoc. 2004 Jul-Aug; 11(4):270-7.

15. Galanter, W.L., Didomenico, RJ and Polikaitis A. *Use of expert system to prevent exacerbation of adverse drug event. J Healthc Inf Manag.* 2002 Fall;16(4):44-9.

16. Galanter, W.L.., Ruiz, O.S., Labotka, R.J. and Arruda, J.A.L. : *Binding of nitrate to renal brush border membranes studied with [14]N nuclear magnetic resonance (NMR).* Biochim. Biophys. Acta , 1237: 16-22, 1995.

17. Galanter, W.L.., Hakimian, M., and Labotka, R.J.: *Structural determinants of substrate specificity of the erythrocyte anion transporter.* Am. J. Physiol., 265 (Cell Physiol. 34): C918-926, 1993.

18. Labotka, R.J., Galanter, W.L., and Misiewicz, V.M.: *NMR spectroscopic studies of Band 3 function using substrate analogs: Substrate specificity, transport kinetics, and anion binding.* Prog. Cell Res. Vol 2, E. Bamberg and H. Passow (Eds.), 121-128, 1992.

19. Galanter, W.L, and Labotka, R.J.: *The binding of nitrate to the human anion exchange protein (AE1) studied with ^{14}N nuclear magnetic resonance.* Biochim. Biophys. Acta 1079: 146-151, 1991.

20. Galanter, W.L., and Labotka, R.J.: *The temperature dependence of human erythrocyte transport of phosphate, phosphite and hypophosphite.* Biochim. Biophys. Acta 1027: 65-71, 1990.

21. Labotka, R.J., Galanter, W.L, and Misiewicz, V.M.: *Erythrocyte bisulfite transport.* Biochim. Biophys. Acta 981: 358-362, 1989.

ABSTRACTS

1. Yang Y, Touchette DR, Tiryaki F, Galanter W et al. *Economic analysis of alvimopan for prevention and management of post-operative Ileus.* Value Health. 2010. Volume: 13 Issue: 3 Pages: A72-A72

2. Walton S, Galanter W, Tiryaki F, et al. *Computerized interventions to obtain interventions to obtain indication information for inpatient prescriptions: A pilot study in drugs frequently used off-label.* Value Health. 2010 Volume: 13 Issue: 3 Pages: A87-A87

3. Patel V, Touchette D, Yang Y, Galanter W et al. *Cost-Effectiveness of strategies for diagnosing heparin-induced thrombocytopenia.* Value Health. 2010. Volume: 13 Issue: 3 Pages: A209-A209

4. Nutescu EA, Bautista A, Gao W, Galanter W, Schumock G, Bookhart B, Moody S, Lambert B. Warfarin *Anticoagulation After Total Hip or Knee Replacement in Real-World Clinical Practice: INR Patterns and Clinical Outcomes*. Chest 2010;138:397A.

5. Nutescu EA, Bautista A, Gao W, Galanter W, et al. *Quality of Oral Anticoagulation Management in Pharmacist Versus Nurse Managed Models of Care.* J Thromb Thrombolysis. 2010. 29:2 p244-244

6. Schiff GD, Duhig JE, Edison MI, Galanter W, et al. *Drug Formulary culture survey: Measuring the temperature of clinicians boiling blood.* J Gen Int Med. 2009. 24 pages63-63. Suppl. 1

7. Duhig J, Edison M, Galanter W, et al. *Conceptual issues in the development of a measure of formulary culture.* Value Health. 2009. 12:3 A8-A8

8. Jao CS, Hier DB, Galanter WL, Valenta AL. *Assessing physician comprehension of and attitudes toward problem list documentation*, AMIA Annual Symposium Proc. 2008;990.

9. Jao CS, Hier DB, Galanter WL. *Automating the maintenance of problem list documentation using clinical decision support system*. AMIA Annual Symposium Proc. 2008;989.

10. Tokumaru SM, Garofalo J, Zadoiskaya D, Galanter W, et al.. *Clinical use of the modification of diet in renal disease (MDRD) equation in dosing of antimicrobials*. Crit Care Med, 2007. 35:12 A241-A241 Suppl. S

11. Galanter, W.L, Mrtek, R and Polikaitis, A.: *Analysis of Compliance with Automated Decision Support Alerts for Contraindicated Medications using Computerized Physician Order Entry (CPOE)*. J Gen Int Med 18:Supp 1:282, 2003.

12. Galanter, W.L and Polikaitis, A.: *Automated Warnings to Reduce Inpatient Administration of Metformin in Patients with Renal Insufficiency.* J Gen Int Med 18:Supp 1:282, 2003.

13. Galanter, W.L, R. Didomenico, R.J. and Polikaitis, A.*: Analysis of medication safety alerts for inpatient Digoxin use with computerized physician order entry.* J Gen Int Med 17:Supp 1:193, 2002.

POSTERS & PRESENTATIONS

1. Galanter WL. Clinical Decision Support to Enhance Patient Safety: Nephrotoxins and Drug Dose Adjustment. National Kidney Foundation, 2011 Spring Clinical Meeting. 2011, April, Las Vegas. Presentation.

2. Yu S, Galanter W, Lin F, Lambert B. The evaluation of clinical laboratory-pharmacy linkage decision support in the use of potassium supplements. ISPOR 16th Annual International Meeting. 2011. Presentation.

3. Galanter W, Walton S, Falck S, Rosencranz H, Adimadhyam S. Using computerized physician order entry of antihypertensive medications to connect indications with prescribing and improve problem list documentation. ISPOR 16th Annual International Meeting. 2011. Poster.

4. Gandhi S, Bursua A, Nutescu E, Galanter, W. *Prescriber adherence to guideline recommendations for use of vitamin K to manage supratherapeutic INR due to warfarin therapy.* ASHP Midyear meeting, Anaheim, CA. 2010. Poster.

5. Galanter W, Lopata M. *COPD or not COPD: That is the question.* Illinois Chapter of ACP Annual Meeting. Springfield, Il. 2010. Presentation.

6. Galanter W. *Markers for the diagnosis of Major Depression and Clinical Coronary Artery Disease: Membrane associated models as diagnostic indicators.* Bio-Molecular Changes in Mood Disorders and their Clinical-Biochemical Classification. Bologna, Italy. 2010. Presentation.

7. Yu S, Galanter W, Lambert B, Schiff G, Borkowsky S. *Consensus List of Priority Drug-Lab Linkages for an Inpatient Asynchronous Alert Program: Results of a Delphi Survey.* American Society of Health-Systems Pharmacists (ASHP) Midyear Meeting. Las Vegas, 2009. Poster.

8. Lambert B, Galanter W, Jung C, Yu S, Schiff G. *Medication-Laboratory Linked Computerized Alerts for Gadolinium and Radiocontrast Imaging in Patients with Chronic Kidney Disease (CKD): Effects on Orders and Study Completion.* American Society of Health-Systems Pharmacists (ASHP) Midyear Meeting. Las Vegas, 2009. Poster.

9. Boddipalli V, Trick W, Lambert B, Kho A and Galanter W. *Patterns of Patient Migration Between Two Urban Public Hospitals in Chicago.* Midwest Society for General Internal Medicine, Chicago, 2009. Presentation.

10. Galanter WL, Liu X, Lambert B. *An Analysis of Computer Alerts Suggesting Oral Medication Use during Computerized Order Entry of Intravenous (IV) Medications.* ACCP/ESCP International Congress on Clinical Pharmacy. 2009. Poster.

11. Galanter WL, C. Jung, Lambert, B.L., Schiff G.D, *The effectiveness of medication-laboratory linked computerized alerts for gadolinium and radiocontrast imaging in patients with chronic kidney disease (CKD).* Midwest Society of General Internal Medicine Annual Meeting, September, Chicago, 2008. Presentation.

12. Galanter WL, Arozullah AM, Tierney WM. *"Comment on Interaction between Medicine and the Marketplace"*, Presentation and Panel. Midwest Society of General Internal Medicine Annual Meeting, September, Chicago, 2008. Panel.

13. Galanter WL, Ethics Grand Rounds, University of Illinois Medical Center at Chicago, Chicago, 2008. Presentation.

14. Galanter WL, *"Industry Influence on Research and Education". In "The interdependence of Healthcare and the Pharmaceutical industry: Friend, Foe, or Something in-Between?"* Annual Ethics conference, University of Illinois Medical Center at Chicago, Chicago, 2008. Presentation.

15. *Evidenced Based Prescribing and the Pharmaceutical Industry,* Special Symposium for Chicago Area Medical and Pharmacy Students, October 2007, Chicago. Presentation.

16. Sarne DH, Hier DB, Jao C, Galanter *WL Improved documentation of endocrine diagnoses using computerized order entry*. The 89th annual meeting of the Endocrine Society. Toronto, Canada June, 2007. Presentation.

17. Desai B, Galanter W, Jenders R, Sittig D, "*Improving Outcomes with Clinical Decision Support*", AMIA Spring Congress, Orlando, 2007. Panel.

18. Galanter, W.L et al. "*Guideline Driven Clinical Decision Support to Improve Venous Thromboembolism Risk Assessment and Pharmacological Prophylaxis at a University Teaching Hospital.*" UHC 2006 Safety and Quality Forum, Baltimore, 2006. Poster.

19. Galanter, W.L "*The use of clinical decision support in the ambulatory setting with an inpatient/ambulatory integrated EMR.*" Illinois Healthcare Information technology Summit, Chicago, 2006. Presentation.

20. Bates DW, Galanter, W.L, Ghandi, T and Welabob, E "*Ask the experts: Patient safety and health IT.*" AHRQ's 2005 Annual patient safety and health information technology conference, Washington, 2005. Panel.

21. Galanter, W.L. "*A Case Study and Literature Review in Automated Clinical Decision Support Implementation to Decrease Medication Errors.*" TEPR (Toward the Electronic Patient Record), Fort Lauderdale, 2004. Presentation.

22. Galanter, W.L. "*A case study in rules implementation*" HIMSS National Meeting, Maryland 2003. Presentation.

23. Galanter, W.L, Keeler J and Townsend, J. *Transforming Healthcare with Information Technology at the University of Illinois Health System.* American Health Information Management Assoc., San Francisco, 2002. Presentation.

WORKSHOPS

1. Galanter, W.L. and Schiff, G. *Healthcare Information Technology.* Chicago Patient Safety Forum. Annual Meeting, Chicago, IL, 2005.

2. Galanter, W.L. and Polikaitis, A *Designing Effective Automated Clinical Decision Support Solutions in the CPOE Environment.* Partnership for Patient Safety (p4ps) symposium, Washington DC, 2002.

EDITORIALS

1. Galanter, W.L., Moja, J and Lambert, B. *Using Computerized Provider Order Entry and Clinical Decision Support to Improve Prescribing in Patients With Decreased GFR.* Am J Kidney Dis. 2010: 56 (5) p 809-812.

2. Galanter, W.L. and Arruda, J.A.L.: *Cellular Adaptation to Hyponatremia: New Insights into the Mechanism.* Kidney 4: 209-210, 1995.

OUTSIDE POSITIONS

Member of Walgreen's Health Initiative (WHI) Pharmacy & Therapeutics Committee

PRESENT FUNDED RESEARCH

Tools for Optimizing Prescribing, Monitoring and Education (TOP-MED), Center for Education and Research on Therapeutics (CERT), Funding Source AHRQ HS016973-01 PI: Bruce Lambert. Co-Investigator: William Galanter, 7/2007-6/2011.

The University of Illinois at Chicago Center for Clinical and Translational Science (CCTS), Funding Source: National Center For Research Resources. 1UL1RR029879-01 PI: Ted Mazzone, Consultant: 7/2009-6/2013

Abbott Labs, Communicating Safe and Appropriate drug use to patients and families. Funding Source: Abbott Labs. PI M. Wolfe. Co-Investigator 1/2010-7/2012

The University of Chicago Center for Education and Research on Therapeutics (CERT), Funding Source AHRQ HS016967 PI: D. Melzer. Co-Investigator: William Galanter, 3/2010-7/2011.

Chicago HIT Regional Extension Center. Office of the National Coordinator for Health Information Technology (ONC). ARRA Health Information Technology Extension Program: Regional Centers. PI: Abel Kho. Co-Investigator: William Galanter, 1/15/2010-1/14/2014.

5/23/11

TO: Mr. Matthew Moriarty
Tucker, Ellis & West LLP
1150 Huntington Building
925 Euclid Avenue
Cleveland, OH 44115-1414

This letter represents my opinions of the case of Mr. Daniel McCornack

Qualification and clinical & research experience with digoxin

I have been practicing medicine since 1993 as a medical resident and since 1996 as a licensed attending physician. My practice is in general internal medicine which entails inpatient care, inpatient medical consultations, ambulatory primary care and ambulatory medical consultations. I care for a significant number of patient with cardiac problems due to a somewhat more elderly patient population in my clinic as well as the tertiary nature of our institution. When I first started practicing I took care of a significant number of patients either waiting for or who had received heart transplants and became comfortable with the management of these patients. This program was stopped at our medical center over 5 years ago and I treat this type of patient less often presently.

I have treated inpatients with significant digoxin toxicity as a resident during my training on our cardiology and cardiac care unit rotations and a have treated a few cases of mild digoxin toxicity on my general medical services over the years. I care for many patients who receive digoxin both for atrial fibrillation and systolic congestive heart failure.

In addition to my clinical use of digoxin, it is a drug that I have helped design interventions for to prevent inappropriate use, specifically overdosing and toxicity[1,2,3]. I am also the Chair of our medical center's Pharmacy and Therapeutics Committee whose role is to oversee medication use at the hospital and clinics. As part of our work, we regularly review adverse drug events reported in our hospital, including those caused by digoxin. I also work for an Agency for Healthcare Research and Quality (AHRQ) funded center on education and research in therapeutics (CERT) regarding the safety of medication use. My CV is available for review starting on page 6.

Expert witness depositions or trial testimony in the past 4 years

None

Charges for expert witness work

$500/hr for review of materials

Materials reviewed

The following are the materials that were reviewed prior to making the opinion presented;

-Depositions

Dr. Gordon Lemm, 10/2/2009
Dr. Richard Mason, 10/1/2009
Mrs. Kathy McCornack, 10/5/2009
Mr. Matthew McMullin 9/29/09
Dr. Lawrence Von Dollen, 10/5/2009

Ladd Gibson + Barbieri

-Clinic Records

Dr. Gordon Lemm, office chart
Dr. Lawrence Von Dollen, office chart

-Other Documents

-Certificate of Death/Autopsy (original)
-Certificate of Death/Autopsy (amended)
-Result from NMS Labs, 6/24/08
-CVS Caremark Letter to Patients RE: Digitek, 5/2008
-FDA Recall Press Release 4/25/2008
-Facts and Myths about Generic Drugs
http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm

Review of Mr. McCornack's medical history

Definite Diagnoses
-Atrial Fibrillation since at least as far back as 1994, from Dr. Lemm's records
-Overweight to Obesity, BMI 29 in 1994, BMI 32 in 2008, from Dr. Lemm's records
-HTN; Pre-Hypertensive or Hypertensive BP's on Multiple Occasions while on Diltiazem from Dr. Lemm's records
-Hyperlipidemia 2008 from Dr. Lemm's records, from multiple labs
    -↓HDL, ↑LDL, ↑Triglycerides
-Gout with hyperuricemia, from labs and Dr. Lemm's records
-Fatty liver CT scan 2005 and periodic mildly elevated AST/ALT, autopsy
-Spinal arthritis, spinal disc Disease, MRI 2005
-Stable mesenteric and retroperitoneal lymphadenopathy of uncertain significance
-Cardiomegaly & LVH-by Autopsy
-CAD-mild-moderate-by autopsy

2-2

Possible Diagnoses
-Possible Glucose Intolerance: Multiple high random or fasting glucose levels, though none in diabetic range, no high GlycoHb
-Possible OSA: Risks Obesity, HTN, Need for pillow to breath better (from Dr. Winkle's notes), use of nostril dilating device (per autopsy and wife's deposition), Snoring per wife.
-Possible ETOH Abuse, reports to Dr. Winkle 2-3 beers a day,
-Nasal congestion, per wife

Recent History prior to his death

The last visit with Dr. Lemm prior to the patients death, 1/8/08, found that his blood pressure was slightly high, 146/86, His weight was 225. His heart rate was not listed. Shortly after this visit he apparently called in to report nausea from simvastatin and was switched to lovastatin. His last lab tests were in December of 2007 and found hyperuricemia and dyslipidemia. His last dig level was done in May of 2007 and was 1.6 ng/ml, similar to what it typically was. His renal function at that time was normal. He was seen by Dr. Von Dollen on 11/29/07 with a complaint of dyspnea on exertion. His pulse and BP were appropriate.

According to his wife's deposition, he had been snoring, not drinking excessively in the time prior to his death. On the day of his death he ate 2 good meals, had at least 1 beer and did not complain of Nausea, vision problems, palpitations or dizziness, though did c/o bloating before bed, after dinner. He might additionally have had a drink with tonic water as suggested by a non zero quinine level despite not taking quinine therapeutically.

Opinion regarding the cause of death

Based on the autopsy findings, Mr. McCornack's prior medical history and his likely clinical status the day of his death as inferred by his wife's testimony and his likely reliable and chronic medication use, the cause of his death was sudden cardiac arrest. His autopsy argues against a massive MI causing pump failure, a pulmonary embolus, aspiration or a stroke. His autopsy did show pulmonary edema, but this may have been related to his sudden cardiac arrest or developed post-mortem.

His pharmacotherapy appeared reasonable. Though there is an interaction between diltiazem and digoxin[4], the patient had been on both agents for a long-time at stable doses with measured digoxin levels within therapeutic range for its use in atrial fibrilation.[4] Though his dose of 0.5 mg/day is higher than typical, due to his size and intact renal function, this dose was acceptable. I do not feel that there was any error made in his therapy for rate control of his AFIB.

The patient had multiple established risk factors for Sudden Cardiac Death[5,6]

-Structural Heart Disease
- Left ventricular hypertrophy due to hypertension found on autopsy
-Myocardial Fibrosis[7] found on autopsy (uncertain etiology)

-Atrial Fibrillation

-Dyslipidemia

-Age >45[8]

-HTN

-obesity

-CAD found on autopsy

-Anti-Arrhythmic Therapy (Digoxin & Diltiazem)

Along with some possible risk factors for Sudden Cardiac Death

-Possibly OSA[9]

-Some type of congenital condition which produced AFIB in his 20's

Based on his stable doses of digoxin and diltiazem and record of reasonable medication compliance, it is unlikely that he was toxic from either medication. Typically the first signs of toxicity from either medication would be bradycardia, especially when taken together as both suppress the AV node and excess diltiazem would cause a further increase of serum digoxin levels. This bradycardia would typically lead to dizziness[3,10]. In addition a high digoxin serum level would likely produce gastrointestinal symptoms of nausea, vomiting or anorexia[3,10]. Per his wife's history, his appetite and lack of complaints the day of his death make his being digoxin toxic highly unlikely.

The levels of his diltiazem and digoxin in the post-mortem axillary sample are not of any value in determining his pre-mortem levels or doses.. First, his diltiazem dose of 480 mg/day, lower than the maximum recommended dose of 540 mg/day[4], should not produce a toxic level in a 225 pound man. Additionally, this dose was stable for over 4 years without any signs of bradycardia in clinic visit records. Similarly, his digoxin levels were very consistent throughout his years on the medication, typically ranging from 1.5 to 1.8 ng/ml. The reported Diltiazem level of 630 ng/ml and digoxin level of 3.6 ng/ml from the 80 hours post-mortem axillary sample were much higher than seems reasonable. The digoxin was twice his typical level during life and the diltiazem was 3 times higher than the reported therapeutic level of 40-200 ng/ml[4]. A person with a twice high-normal digoxin and three times high-normal diltiazem level would have likely been bradycardic and dizzy and suffering from anorexia and nausea. In addition, there was no evidence from the remaining digoxin tablets that any had more than the usual dose of digoxin in them or were any larger than usual.

It is much more likely that these levels from the 80 hours post-mortem axillary sample cannot be associated with pre-mortem pharmacologic levels due to the duration of time

between the death and the sample being removed as well as redistribution and proximity of the axillary vessel to the heart[11-15]. This literature consistently shows that redistribution plays a large role in post-mortem levels for certain drugs, particularly digoxin. The NMS report itself suggested this phenomena for the diltiazem, though interestingly did not mention this for digoxin as suggested in the literature noted and in Mr. McMullin's deposition. In my opinion to a reasonable degree of medical certainty Mr. McCornack was not digoxin toxic or had an elevated serum digoxin concentration prior to his death. He would have been no more likely to have died from a complication of digoxin than anyone else with a similar medical history taking the medication as suggested and with levels in the normal therapeutic range for the indication of atrial fibrillation.

The patient also may have had some congenital susceptibility to arrhythmias as evidenced by the development of lone atrial fibrillation in his early 20's, which is very unusual[16]. In addition, he was found to have myocardial fibrosis on his autopsy with in some literature has been associated with Sudden Cardiac Death[7] and is a form of structural heart disease.

In summary, the patient had multiple risk factors for sudden cardiac death and in my opinion to a reasonable degree of medical certainty is the most likely cause of his death. Any of the risk factors mentioned, in combination or alone, could have contributed to this Sudden Cardiac Death, including the possibility of a small myocardial infarction, not visible to the pathologist, but in an arrhythmogenic location of the myocardium.

William Galanter, M.D, Ph.D

Literature/reference material

1) Galanter WL, Polikaitis A, DiDomenico RJ. Preventing exacerbation of an ADE with automated decision support. J Healthc Inf Manag. 2002 Fall;16(4):44-9.

2) Galanter WL, Polikaitis A, DiDomenico RJ. A trial of automated safety alerts for inpatient digoxin use with computerized physician order entry. J Am Med Inform Assoc. 2004 Jul-Aug;11(4):270-7.

3) Bauman JL, Didomenico RJ, Galanter WL. Mechanisms, manifestations, and management of digoxin toxicity in the modern era. Am J Cardiovasc Drugs. 2006;6(2):77-86.

4) MICROMEDEX® 1.0 (Healthcare Series), Thomson Reuters Healthcare

5) Up to Date v19.1, Overview of Sudden cardiac arrest (SCA) and sudden cardiac death, accessed 4/2011.

2-5

6) Adabag, A. S. et al. Sudden cardiac death: epidemiology and risk factors. Nat. Rev. Cardiol. 2010. 7: 216–225.

7) Lecomte D, Fornes P, Fouret P, Nicolas G. Isolated myocardial fibrosis as a cause of sudden cardiac death and its possible relation to myocarditis. J Forensic Sci. 1993 May;38(3):617-21.

8) Chugh, S. S. et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate based review in a large US community. Journal of the American College of Cardiology. 2003. 44(6): 1268–1275.

9) Gami AS, SomersVK. Implications of Obstructive Sleep Apnea for Atrial Fibrillation and Sudden Cardiac Death. J Cardiovasc Electrophysiol. 2008. Vol(19):997-1003

10) Abad-Santos F, Carcas AJ, Ibáñez C, Frías J. Digoxin level and clinical manifestations as determinants in the diagnosis of digoxin toxicity. Ther Drug Monit. 2000 Apr;22(2):163-8.

11) Yarema MC, Becker CE. Key Concepts in Postmortem Drug Redistribution. Clinical Toxicology. 2005. 43:235-241.

12) Koren G, MacLeod SM. Postmortem redistribution of digoxin in rats. J Forensic Sci. 1985 Jan;30(1):92-6.

13) Koren G, Beatie D, Soldin S, Einerson TR, MacLeod S. Interpretation of elevated postmortem serum concentrations of digoxin in infants and children. Arch Pathol Lab Med. 1989 Jul;113(7):758-61.

14) Drummer, OH. Postmortem drug analysis: analytical and toxicological aspects. Therapeutic Drug Monitoring. 2002. 24:199-209.

15) O'Sullivan JJ, McCarthy PT, Wren C. Differences in amiodarone, digoxin, flecainide and sotalol concentrations between antemortem serum and femoral postmortem blood. Hum Exp Toxicol. 1995 Jul;14(7):605-8.

16) Hiss RG, Lamb LE. Electrocardiographic findings in 122,043 individuals. Circulation. 1962;25:947.

Sudden cardiac death: epidemiology and risk factors

A. Selcuk Adabag, Russell V. Luepker, Véronique L. Roger and Bernard J. Gersh

Abstract | Sudden cardiac death (SCD) is an important public-health problem with multiple etiologies, risk factors, and changing temporal trends. Substantial progress has been made over the past few decades in identifying markers that confer increased SCD risk at the population level. However, the quest for predicting the high-risk individual who could be a candidate for an implantable cardioverter-defibrillator, or other therapy, continues. In this article, we review the incidence, temporal trends, and triggers of SCD, and its demographic, clinical, and genetic risk factors. We also discuss the available evidence supporting the use of public-access defibrillators.

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Introduction

Sudden cardiac death (SCD) is a common and devastating event, often occurring in the prime of life and having profound consequences for surviving members of the individual's family. Out-of-hospital SCD is the cause of more than 60% of all deaths from cardiovascular disease, which is the leading cause of death worldwide.[1–4] In the past few decades, substantial progress has been made in our understanding of SCD and in its prevention and management. Multiple clinical, structural, autonomic, and genetic risk factors have been identified and the use of automated external defibrillators (AEDs) and implantable cardioverter-defibrillators (ICDs) has increased. However, SCD continues to be an important public-health problem, largely because the majority of SCDs occur in individuals without previously diagnosed heart disease who do not meet the high-risk criteria defined by clinical trials and cohort studies.[5,6] Moreover, risk stratification of individuals lacks specificity and research into the genetics of sudden cardiac death is still at a very early stage. Thus, prevention of SCD hinges upon public-health interventions focused on the primary and secondary prevention of cardiovascular diseases.

The epidemiological, or population, approach to the investigation of cardiovascular disease was established in the 1940s and 1950s by Dawber and coworkers in the Framingham Heart Study and by Keys and colleagues in the Seven Countries Study.[7] These investigations provided community-based data on the incidence, course, and prognosis of cardiovascular disease and helped to identify risk factors and gain insights into pathogenesis.[7] Much of the established knowledge on SCD, including its genetic origins, comes from epidemiological studies. Moreover, owing to temporal trends in the incidence and prognosis of coronary heart disease (CHD), diabetes mellitus, hyperlipidemia, and obesity, the epidemiology of SCD has also seen substantial fluctuation. In this article, we review the incidence, temporal trends, triggers, and time-dependency of SCD. We will also summarize the demographic, clinical, and genetic risk factors for SCD and the evidence supporting the use of public-access defibrillators.

Definition and incidence

The widely-accepted definition of SCD is unexpected death that occurs within 1 h from the start of symptoms when death is witnessed, and within 24 h of being seen alive and well when it is unwitnessed.[8] Most deaths that meet this definition are caused by cardiac arrhythmias, including those resulting from acute myocardial infarction. However, other potential causes, such as stroke, pulmonary embolism, aortic rupture, and drug or alcohol intoxication, need to be considered, although excluding these noncardiac causes of death is often difficult. The majority of SCDs are not witnessed and, if they are observed, the accounts obtained from witnesses may be unreliable. Furthermore, in many cases, medical records are unavailable, autopsy is not performed, and the cause of death given on the death certificate is speculative of the underlying event.[2,9,10]

The incidence of SCD has been estimated to be between 300,000 and 450,000 annually in the US.[1,3,11] These retrospective assessments are based on the assumption that all out-of-hospital deaths, for which CHD is given as the primary cause of death on the death certificate, are SCDs. This approach has been shown to be sensitive, but not specific, for identifying SCD.[11–14] Thus, these retrospective figures are likely to be an overestimate of the true SCD incidence in the community. Conversely, limiting the definition of SCD to deaths that occur within 1 h of symptom onset might be too restrictive and exclude many unwitnessed cases. The incidence figures obtained from

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studies of sudden cardiac arrest (range 40–90 SCDs per 100,000 individuals), which are based on data collected from first responders, could also be an underestimate because these statistics do not include unwitnessed SCDs or deaths not attended by emergency medical personnel.[15–17] Thus, multiple sources of ascertainment are needed in order to determine the true incidence of SCD.[5] Indeed, in two prospective community studies that used multiple sources to identify SCD, the annual incidence of SCD was lower than previously reported estimates—100 deaths per 100,000 among 20–75 year-old residents of Maastricht, the Netherlands,[18] and 53 deaths per 100,000 among residents of Multnomah County, OR, USA.[11] Data from community studies in China and Ireland, which also used multiple sources to identify SCD, indicate that SCD incidence is 40–50 per 100,000 persons annually.[19,20] Furthermore, SCD occurred in 6.8% of the ~5,000 individuals in the Framingham Heart Study over ~50 years of follow-up[13,21] and in 4.4% of the ~7,000 individuals in the Paris Prospective Study over 23 years of follow-up.[22] On the basis of these figures, the annual incidence of sudden cardiac death in the US (total population ~320 million) would range between 180,000 and 250,000 cases per year.[2]

Deaths from CHD have declined markedly over the past several decades. This change is largely attributable to improvements in the primary and secondary prevention of CHD and to progress in acute treatment strategies.[23–25] The incidence of SCD has also declined, in parallel with the decline in CHD mortality.[14,21,23] A 49% decrease in the risk of SCD over 50 years was observed in the Framingham Heart Study.[21] The temporal decline in SCD was more pronounced among patients with known CHD than in those without CHD,[14] and was greater among men than women.[1] Despite the reduction in the absolute rate of SCD, the incidence of SCD as a proportion of overall cardiovascular deaths has increased, because in-hospital mortality has declined more rapidly than out-of-hospital mortality (Figure 1). Therefore, SCD now accounts for more than half of all CHD deaths.[1] These trends underscore the need for a renewed emphasis on primary prevention of CHD. Although survival after cardiac arrest has not changed appreciably in the past three decades, the long-term prognosis of those who survive to hospital discharge after a sudden cardiac arrest has improved.[26] In Olmsted County, MN, USA, the 5-year survival of patients who had an out-of-hospital cardiac arrest with ventricular fibrillation and survived to be discharged from the hospital was 79%, equal to age, sex, and disease-matched individuals without cardiac arrest.[26] These data highlight the successes of secondary prevention and ICD therapy.[27]

Age, sex, and race

The age distribution of SCD demonstrates peaks during infancy and after the age of 45 years (Figure 2). In adults, the risk of SCD increases with age and mirrors the incidence of CHD.[8,11] In the young (<30 years of age), however, the most common causes of SCD include cardiomyopathies, coronary anomalies, primary arrhythmogenic disorders, and drug abuse, rather than CHD.[28] Middle-aged men have a fourfold greater risk of SCD when compared with women of the same age.[8] However, this difference decreases with age, possibly as a result of the postmenopausal development of CHD in women. Furthermore, an increase in the proportion of out-of-hospital CHD deaths occurring in women has been observed since the 1970s.[11,29] This shift is attributed to a lower rate of decline in total mortality and SCD incidence among women in comparison with men, for reasons that are as yet unclear (Figure 1).[1,15]

Racial differences in the incidence of SCD have not been well investigated. The available data from death certificates suggest that, for both sexes, SCD is more common among black Americans than white and Hispanic Americans.[1,30] Moreover, in the US, black patients with in-hospital cardiac arrest are significantly less likely to survive to hospital discharge, are less likely to survive after cardiopulmonary resuscitation (CPR),

Key points

- Sudden cardiac death (SCD) is a common public health problem that causes more than 60% of all deaths from cardiovascular disease
- Coronary heart disease underlies 80% of SCD cases; SCD is the first manifestation of heart disease in 50% of these individuals
- Prospective surveillance programs, using multiple sources to identify cases of SCD, would enable more accurate determination of SCD burden in the community
- Demographic, clinical, structural, laboratory, and genetic risk factors lack the specificity to identify individuals at high risk for SCD when used alone; multimarker SCD risk scores may improve SCD prediction
- The risk of SCD after a coronary event changes with time, therefore, dynamic risk-profiling is important
- Survival after sudden cardiac arrest is ~5% and many individuals do not receive cardiopulmonary resuscitation or defibrillation; educating the public to use automated external defibrillators will be important to improving survival

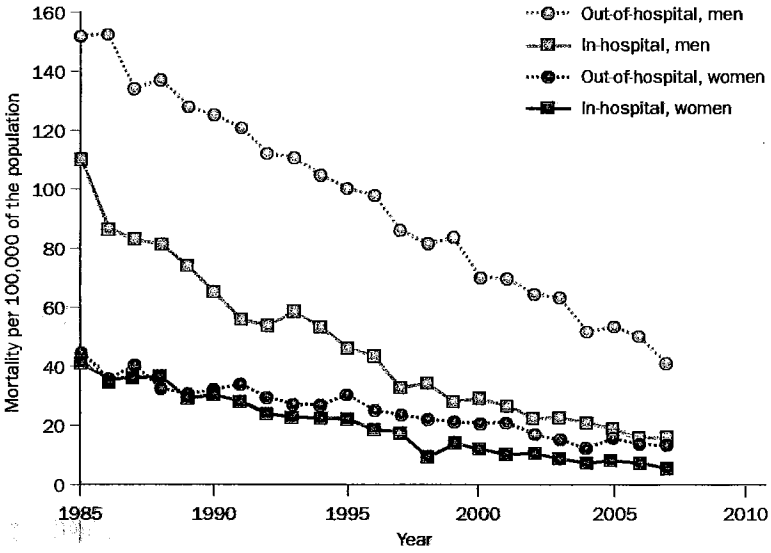

Figure 1 | Temporal trends in in-hospital and out-of-hospital cardiovascular mortality among men and women living in Minneapolis–St Paul, MN, USA.

3-2

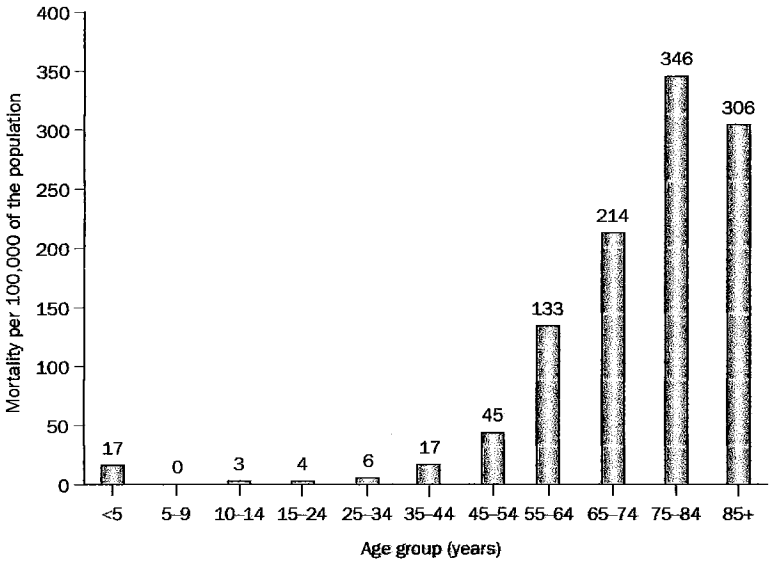

Figure 2 | Age distribution of sudden cardiac death among residents of Multnomah County, OR, USA (population 660,486) between 1 February 2002 and 31 January 2003. Reprinted from the *Journal of the American College of Cardiology*, 44(6), Chugh, S. S. *et al.* Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large US community. 1268–1275 © 2004 with permission from Elsevier and the American College of Cardiology.

and have lower rates of postresuscitation care than white patients.[31] This racial difference in outcomes substantially decreases after adjustment for the effect of the hospital site at which patients received care.[31]

Temporality and variation in rhythm

Approximately 80% of all SCDs occur in the home and around 60% are witnessed.[18,32–34] Several studies have demonstrated that there is a heightened risk of SCD on Mondays, in the early hours of the morning (0500 h to 0900 h), and during the winter months, with particular association with lower temperatures (<0 °C).[35–38] These temporal variations are thought to be secondary to increased ischemia owing to factors such as increased adrenergic activity. Overall, relatively few people who experience a sudden cardiac arrest receive CPR from a bystander, and this action is more likely to occur in public places than in the home.[18,32,39]

In most cases, SCD is thought to be the consequence of ventricular tachycardia, degenerating to ventricular fibrillation and subsequent asystole. In a study of confirmed cardiac arrest, where a defibrillator was used within 3 min of cardiac arrest, the initial rhythm was ventricular tachycardia or fibrillation in 71% of individuals, asystole in 18%, and pulseless electrical activity in 11%.[40] However, there was a 43% decline in the incidence of ventricular fibrillation as the causative rhythm disturbance between 1980 and 2000 among patients treated for out-of-hospital cardiac arrest in Seattle, WA, USA.[15] In the year 2000, only 41% of the cardiac arrests were due to ventricular fibrillation.[15] Similar reductions in the incidence of ventricular fibrillation in Finland and Sweden have also been reported.[41,42] The reasons for this change are speculative, but could be related to aging of the population with a higher prevalence of comorbidities, including heart failure. Whereas ventricular fibrillation can be a manifestation of ischemia, asystole is often the initial rhythm in cardiac arrest caused by heart failure.

SCD after myocardial infarction

Acute ST-segment elevation myocardial infarction (MI) is associated with ventricular arrhythmias and cardiac arrest. The risk of SCD is highest in the first 30 days after MI, and decreases gradually with time.[43–45] Among survivors of MI with left ventricular (LV) dysfunction or heart failure, the risk of SCD has been reported to be 1.4% in the first 30 days, but 0.14% per month after 2 years.[44] In a community-based cohort, the risk of SCD was 1.2% within the first month after MI, markedly exceeding the incidence in the general population[43] (Figure 3). Thereafter, however, the SCD risk declined markedly to 1.2% per year, which is lower than expected in the general population (~3% per year). This risk reduction is largely the result of secondary prevention measures, the early death of patients with severe disease, or both. Classic teaching is that arrhythmias in the first 12–24 h after MI do not predict SCD, although this notion has been challenged.[46] Current practice guidelines recommend assessing LV function 6 weeks after MI to determine whether ICD implantation for primary prevention of SCD is recommended. Zaman *et al.* showed that ventricular tachycardia, induced during programmed electrical stimulation (which was performed to risk stratify patients early after MI and subsequent revascularization), identifies those at high risk of SCD who are likely to benefit from ICD implantation.[47]

The incidence of SCD after MI has decreased over the years in parallel with the decline in CHD mortality and SCD in the general population.[43] In a study by Marcus and colleagues, which was conducted in the 1980s, approximately 10% of MI survivors died suddenly during the 4-year follow-up period.[48] This rate has now decreased to less than 1% per year among patients who receive optimal medical therapy and revascularization.[49,50] Indeed, in Olmsted County, MN, USA, the risk of SCD after MI has declined by more than 40% over the past 25 years.[43] This decline predates the widespread use of ICDs, but parallels the increased use of reperfusion therapy and secondary prevention measures after MI. In the 1980s, 40–50% of deaths after MI were caused by sudden cardiac arrest,[48,51] but the proportion of SCDs has decreased to 20–30% in more contemporary cohorts.[43,49,50]

The concept of 'dynamic risk profiling' after MI relates to changes in the presence and power of risk markers over time, including LV remodeling, changes in the anatomical and electrophysiological properties of the myocardial scar, and progression of CHD.[6] Indeed, the risk of SCD beyond the first 30 days after MI is markedly increased by the presence of concomitant heart failure and ischemic events, which occur frequently during follow-up.[43,50–53] Among participants of MADIT-II[52] who were randomly assigned to receive an ICD, heart failure and recurrent ischemia were associated with a 2.5-fold

3-3

and 1.5-fold higher risk of appropriate shocks for ventricular tachycardia or fibrillation, respectively. Also, among residents of Olmsted County, MN, USA who survived an MI, the occurrence of heart failure was associated with a fourfold increase in SCD risk, with the majority of SCDs occurring within 30 days of the heart failure episode.[43] These findings underscore the importance of continued surveillance and dynamic risk profiling of patients after MI.

Risk factors for SCD

Clinical risk predictors

Most people who suffer SCD have CHD. In around 50% of cases, SCD is the first clinical manifestation of heart disease.[18] Therefore, it is not surprising that clinical risk factors for SCD are also predictors of CHD-related death and all-cause mortality.[6] Indeed, risk factors such as, older age, male sex, cigarette smoking, hypertension, diabetes mellitus, hypercholesterolemia, obesity, and family history of CHD have all been associated with an increased risk of SCD.[8,22,53–55] Although these risk factors are powerful predictors at a population level, they are not specific enough to determine risk in an individual patient because of relatively low event rates (that is, low absolute risk). Additional SCD risk factors, such as LV dysfunction, history of heart failure, LV hypertrophy, poor functional status, elevated heart rate, an abnormal electrocardiogram, and abnormal autonomic markers, also lack the specificity to discriminate SCD from non-sudden death.[3,8,56–59] Only a small proportion of SCDs occur in patients with known markers of high-risk for arrhythmia[5] (Figure 4). Thus, in the absence of specific single markers, a multimarker strategy may be necessary to identify individuals with high SCD risk. Indeed, Buxton *et al.*[56,57] and others have created multivariable risk algorithms for SCD that are based on retrospective analyses of large clinical trials.[60–62] The markers in their algorithm were age, functional class, history of heart failure, nonsustained ventricular tachycardia, LV ejection fraction, LV conduction abnormalities, inducible sustained ventricular tachycardia, and atrial fibrillation. However, these algorithms are yet to be validated prospectively in large population studies.

Autopsy findings

Autopsy studies have shown that approximately 80% of adults who suffer SCD have severe CHD,[8,63] 10–15% have dilated or hypertrophic cardiomyopathy, and 5–10% have structurally normal hearts, suggesting that a primary arrhythmogenic disorder was the cause of death.[1] A substantial proportion (10–80%) of those with CHD have intracoronary plaque rupture, thrombus formation, or both, which are indicative of an acute coronary syndrome,[63–65] and around 30% have myocardial scar from a previous MI, creating a substrate for ventricular tachycardia.[65] LV hypertrophy, inflammation, infiltrative diseases (such as amyloidosis), and interstitial fibrosis are other structural abnormalities that create a potential substrate for ventricular arrhythmias.[66–68] Although clinical reports suggest that cardiac structural abnormalities

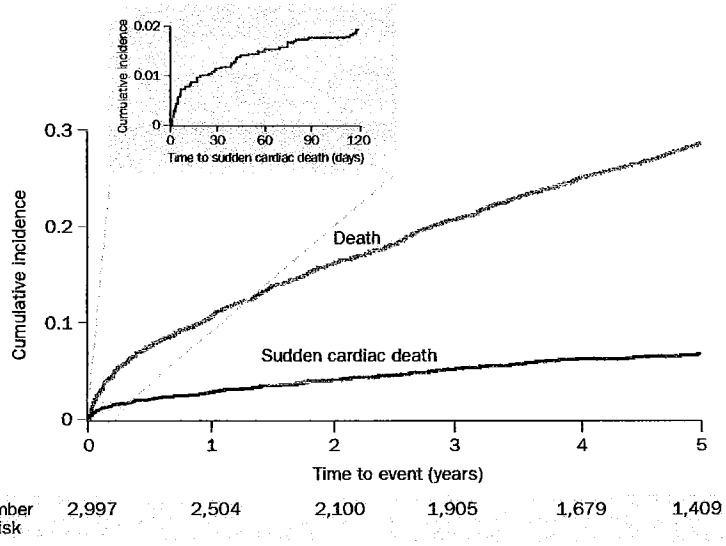

Figure 3 | Cumulative incidence of sudden cardiac death and all-cause mortality after myocardial infarction among residents of Olmsted County, MN, USA. The shaded area represents the cumulative incidence of sudden cardiac death during the first 120 days after the index myocardial infarction. Reproduced from Adabag, A. S. *et al.* Sudden death after myocardial infarction. *JAMA* 5 November 2008; 300(17), 2022–2029. © 2008 American Medical Association. All rights reserved.

are absent in up to 10% of survivors of sudden cardiac arrest and those who died suddenly,[2,3,8] careful evaluation of clinical history has revealed potential risks for SCD in the majority of these patients.[66] For example, Shen *et al.* reported that 33% of 20–40 year-olds who suffered SCD had a history of cocaine abuse.[28]

Heart failure

More than 5 million people in the US have heart failure, and around 600,000 new cases occur annually.[69] The process of remodeling in heart failure, which encompasses cellular, structural, and electrical changes in the myocardium, and neurohormonal activation, provide a suitable milieu for arrhythmogenesis.[70] Consequently, clinical heart failure leads to a fivefold increase in SCD risk.[43,71] Furthermore, SCD accounts for 30–50% of all deaths in patients with heart failure.[71] With advancing symptoms and decompensation of heart failure, however, the proportion of deaths that are classified as SCD decrease whereas those caused by heart failure itself increase. Reports suggest that 64% of patients with mild symptoms of heart failure die suddenly as opposed to 33% of those with severe symptoms.[5] Increased levels of brain natriuretic peptide—a biomarker secreted in response to ventricular stretch—was associated with an increased risk of SCD in patients with LV dysfunction and heart failure, and among women who participated in the Nurses' Health Study.[72–74]

Severe LV dysfunction, caused by ischemic or non-ischemic cardiomyopathy, is also a marker of elevated SCD risk.[75] In current practice guidelines, an LV ejection fraction of less than 35% is a major criterion for ICD therapy.[75] However, only 20–30% of ICD recipients in randomized clinical trials receive appropriate ICD shocks

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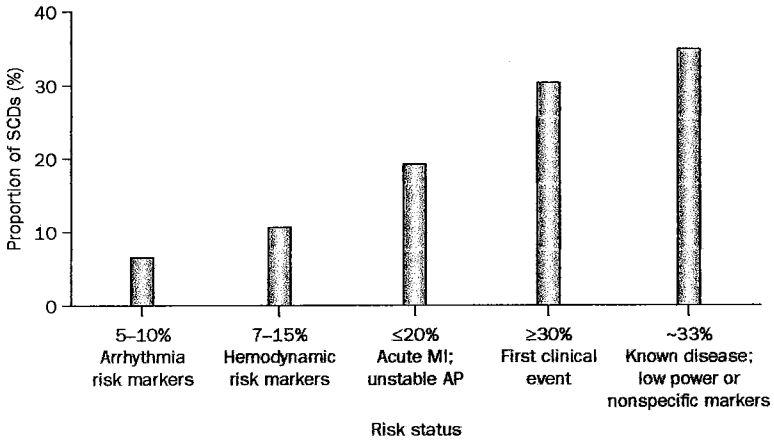

Figure 4 | Distribution of clinical status of individuals who suffer sudden cardiac death. Abbreviations: AP, angina pectoris; MI, myocardial infarction; SCD, sudden cardiac death. Reprinted from *Journal of the American College of Cardiology* 54(9), Myerburg, R. J., Reddy, V. and Castellanos, A. Indications for implantable cardioverter-defibrillators based on evidence and judgment. 747–763. Copyright (2009), with permission from Elsevier and the American College of Cardiology.

over 4 years of follow-up, reducing the positive predictive value of LV dysfunction as a marker.[76,77] Furthermore, in population cohort studies, approximately 65% of those who suffer SCD have either normal or mildly depressed LV function (that is, an ejection fraction of 35–50%).[18,78,79] Therefore, severe LV dysfunction alone is not a sufficiently specific marker for SCD, but could be useful when used with other predictors or as part of a multivariable risk score.[56,61,62]

Electrocardiographic risk predictors

Abnormalities on a 12-lead electrocardiogram raise the suspicion of underlying structural or genetic heart diseases associated with SCD (Box 1). Pathologic Q waves or dynamic ST-segment changes on electrocardiography are indicative of CHD, whereas increased R-wave voltage or prolonged QRS duration are signs of LV hypertrophy and cardiomyopathy, respectively. Left bundle (but not right bundle) branch block or LV hypertrophy on electrocardiography are associated with a mildly increased risk of SCD (hazard ratio ~1.5 for both).[58,80] In addition, prolonged QRS duration was associated with SCD and ventricular tachyarrhythmias in two large clinical trials,[81,82] and Das *et al.* have suggested that fragmented QRS on electrocardiography is a marker of structural heart disease and predicts SCD.[83]

The electrocardiogram is particularly helpful in diagnosing primary arrhythmogenic disorders, such as the long and short QT syndromes, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and Wolff–Parkinson–White syndrome, all of which are associated with SCD.[8,84,85] These conditions are rare in the community; however, QT-interval prolongation and dispersion, which are more common and indicate prolonged repolarization, have also been associated with SCD in the general population.[2,86,87] Individuals with a corrected QT interval of greater than 440 ms have a 2.3-fold higher risk of SCD than those with corrected QT interval of less than 440 ms, independent of age, sex, heart rate, and drug use.[85] Furthermore, those with QT prolongation in the absence of QT prolonging drugs or diabetes have a fivefold increased risk of SCD.[87]

Abnormal heart rate profile on exercise electrocardiography, late potentials on signal-averaged electrocardiography, microvolt T-wave alternans, and reduced heart rate variability on Holter electrocardiography have all been shown to correlate with increased risk of SCD.[46,88,89] However, these specialized markers have a high negative predictive value and a low positive predictive value. Thus, SCD risk is low with a negative test, but indeterminate with a positive test.

Socioeconomic and psychosocial risk predictors

Low socioeconomic status is associated with an increased prevalence of risk factors for cardiovascular disease, CHD, and cardiovascular mortality.[90] The incidence of out-of-hospital cardiac arrest and SCD are also higher in areas of socioeconomic deprivation than in more affluent areas.[2,91,92] The effect of socioeconomic status on SCD is more marked among individuals younger than 65 years of age.[92] The mechanisms underlying the apparent association between socioeconomic status and SCD probably reflect a confluence of behavioral, environmental, and coronary risk factors, such as smoking and reduced access to health care.

Psychosocial risk factors, such as social isolation, a high degree of life stress, and substantial life changes have also been associated with SCD.[8,93] Among men with complex premature ventricular contractions after MI, those with lower educational status had threefold higher mortality than those who were better educated.[93] Furthermore, individuals who have suffered SCD have been reported to have experienced more life-changing events during the 6 months before SCD than controls.[8] Hostility and history of psychiatric diseases were also associated with an increased prevalence of SCD.[94] Whether the elevated risk of SCD is associated with the presence of CHD risk factors (such as smoking) in this population, or with the potential arrhythmic consequences of psychoactive medications, is yet to be established.[94]

Genetic risk predictors

The genetics of rare arrhythmogenic syndromes associated with SCD, such as long QT syndrome, have been recognized for several decades; however, the possibility of a genetic basis for SCD in the general population has only been proposed in the last 10 years.[22,95–97] Jouven *et al.* found that SCD risk was twofold higher if an individual had one parent who died suddenly, and ninefold higher if both parents died suddenly.[22] This effect was independent of parental history of MI. Dekker *et al.* reported that family history of SCD (odds ratio ~2.5) and cumulative ST-segment deviation (odds ratio ~1.5) were the only differences between patients who had cardiac arrest with acute MI and those who did not.[95] These data, therefore, indicate that heritable factors play an important role in determining SCD risk, possibly because of shared genes that increase vulnerability to life-threatening

3-5

arrhythmias. The selective effect of family history on SCD risk, independent of MI, suggests that at least some genetic factors may specifically predispose the individual to fatal arrhythmias, rather than the effect being mediated through an increased risk of CHD. Furthermore, the increase in SCD risk with a greater number of relatives affected is consistent with a complex genetic architecture, in which susceptibility alleles increase risk additively.[98]

The genetic origins of complex events, such as SCD, can be explained either by rare variants with strong effects, rare variants with modest effects, or common variants with modest effects.[89] Rare variants with strong effects have been identified in genes that lead to uncommon inherited cardiac diseases associated with increased risk of ventricular arrhythmias and SCD, such as long and short QT syndromes, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia.[89] Molecular characterization of these diseases has provided the evidence that mutations in specific genes predispose the individual to SCD and has increased our understanding of the mechanisms of arrhythmogenesis. However, these rare mutations are subject to negative selection of allele frequency and contribute little to the burden of SCD in the general population.[89,98]

Rare variants with modest effect are 'less malignant' variations in the genes responsible for the arrhythmogenic disorders, such as long QT syndrome. These relatively unimportant changes could increase susceptibility to arrhythmias in the general population. Indeed, evidence from autopsy series suggests that those who have suffered apparently idiopathic SCD might harbor mutations in these candidate genes, particularly those described in long QT syndrome.[99–103] Chugh *et al.* identified a mutation in *KCNH2 (HERG)*, which encodes a voltage-gated potassium channel, in 16.7% of 12 adults who had suffered SCD.[99] Tester *et al.* showed that 30% of 49 individuals who died of unexplained sudden cardiac arrest harbored a mutation in one of the genes associated with long QT syndrome, and 14% had a mutation in the ryanodine receptor gene (*RYR2*).[100,101] Furthermore, in the Nurses' Health Study, rare missense variants in *SCN5A*, which encodes the sodium channel alpha subunit, were detected in 10% of participants who died suddenly versus 1.6% of matched controls.[102] In a community-based study in Hennepin County, MN, USA, missense mutations in genes associated with long QT syndrome, all localized to *SCN5A*, were found in 6% of individuals who suffered SCD.[103] These data support the concept that rare variants with modest effects might not produce an identifiable clinical syndrome in isolation, but could predispose the individual to acquired long QT syndrome and SCD after exposure to a secondary risk factor, such as a QT-interval-prolonging medication.[89]

Of potentially greater relevance to the general population are common genetic variants with modest effects that could contribute incrementally to SCD risk. Individuals with these gene variants may survive to reproductive age and, therefore, the variant remains unaffected by negative selection and can reach relatively high allele frequency in the population. Splawksi *et al.* identified the S1102Y variant of the sodium channel gene *SCN5A* in 57% of 23 black patients with an arrhythmia, syncope, and QT prolongation versus 13% of healthy control individuals.[104] This variant allele accelerates sodium-channel activation, potentially increasing the likelihood of arrhythmia. In a follow-up autopsy study, the S1102Y allele was found in the *SCN5A* gene of 28% of black individuals without structural heart disease who had suffered SCD, and in only 5.6% of controls who had died suddenly from noncardiac causes.[105] Common genetic variants in isolation are unlikely to cause SCD because, if they did, strong selection pressure would reduce their allele frequency substantially.[89,98] More probably, these variants contribute only incrementally to the overall risk of SCD by reducing 'repolarization reserve' and predisposing some individuals to SCD through interactions with other risk factors such as ischemia, hypokalemia, or drug exposure.

As discussed above, QT prolongation is a consistent risk factor for SCD in the general population.[86,106] The QT interval—adjusted for heart rate, age, and sex—is normally distributed in the general population and around 35% of QT interval variability is attributable to genetic factors.[107] Common variants in the *KCNH2* (voltage-gated potassium channel) and *NOS1AP* (nitric oxide synthase 1 adaptor protein) genes influence QT interval duration.[106,108–110] However, these variants have a modest effect on QT interval at baseline (ranging from 6 to 12 ms) and an external influence is also likely to be necessary to prolong the QT interval to a degree where the SCD risk increases substantially. Therefore, the available evidence suggests that inheritable factors are partly involved in the pathogenesis of SCD, but the genetic basis of these events in the population is multifactorial and potentially includes the genetics of atherothrombosis and plaque stability, among other factors.[111,112]

Box 1 | Electrocardiographic markers of SCD risk

12-lead electrocardiography
- Pathologic Q waves or dynamic ST-segment changes
- Prolonged QRS duration
- Increased R-wave voltage
- Fragmented QRS
- Prolonged QT interval

Exercise electrocardiography
- Reduced heart-rate recovery
- Reduced functional capacity
- Increased ventricular ectopy
- T-wave alternans

Signal-averaged electrocardiography
- Late potentials

Ambulatory Holter electrocardiography
- Reduced heart-rate variability
- Nonsustained ventricular tachycardia

Triggers of SCD

The current paradigm in SCD requires the presence of an abnormal myocardial substrate, such as CHD,

3-6

and a transient external or internal factor that triggers cardiac arrest. While the abnormal substrate is identifiable in most cases of SCD, the transient triggers are not because a substantial proportion of deaths are unwitnessed or the accounts of the witnesses are biased. The majority of individuals who suffer a witnessed SCD report angina, dyspnea, nausea or vomiting, dizziness or syncope, and 'not feeling well' before cardiac arrest.[18,32] In a community-based SCD study in Hennepin County, MN, USA, we observed that 50% of those who died from a sudden cardiac arrest had taken analgesic and anti-inflammatory medications shortly before death, suggesting that they were not feeling well.[103] In the same study, around 30% of those who suffered SCD had smoked in the hours before death, and this risk factor may have acted as a trigger. Indeed, cigarette smoking promotes platelet aggregation and catecholamine surges, increasing the likelihood of plaque rupture, coronary vasospasm, and thrombus formation.[64,113] Symptoms, therefore, often seem to be present before cardiac arrest, but are tolerated for prolonged periods of time (~75 min) particularly when the individual is at home.[32] These findings underscore the importance of educating patients with cardiovascular disease and their families about the warning signs of impending sudden cardiac arrest and promoting early intervention.

Public-access defibrillators

Prompt defibrillation of an individual who has suffered a sudden cardiac arrest is the most important determinant of survival. For every minute that passes between cardiac arrest and defibrillation, survival decreases by 7–10% without CPR, and by 3–4% with immediate CPR.[114] After 10 min or longer without defibrillation, 95% of patients die. The response times for emergency medical services in most areas of the US are typically 8–15 min; therefore, overall survival after sudden cardiac arrest in most communities is only 5–10%.[33,114] However, patients who are defibrillated within 10 min of cardiac arrest have a 40% chance of surviving to hospital discharge neurologically intact.[26] The long-term survival and quality-of-life scores of these patients are equal to age-matched and sex-matched individuals in the general population.[26]

AEDs are portable, computerized devices that can analyze cardiac rhythm accurately and deliver a biphasic electrical shock in cases of ventricular tachycardia or fibrillation. Studies have shown that AEDs can be easily operated by untrained lay persons.[115,116] Indeed, AED programs at airports and casinos have been associated with 50–75% survival among individuals who suffer an out-of-hospital cardiac arrest when immediate CPR is provided and defibrillation occurs within 3–5 min of cardiac arrest.[40,114,116,117] In the Public Access Defibrillation Trial,[118] volunteer responders from ~1,000 community locations, such as shopping malls or apartment complexes, were randomly assigned to undergo training in CPR alone or to training in CPR plus AED use. Individuals who suffered a cardiac arrest in these communities were twice as likely to survive to hospital discharge when the responder was trained in CPR plus AED use than if the responder was trained in CPR alone.[118] Currently, all federal buildings and airports in the US, and passenger airplanes run by US-based airlines, are legally required to have AEDs. Health and fitness facilities, and schools are also recommended to have AEDs, and many states are passing laws mandating AEDs in public places.

Since most SCDs occur in the home, the Home Automated External Defibrillator Trial[119] was performed to assess whether AED placement at homes of individuals who are at increased risk of SCD would save lives. About 7,000 patients with prior MI who were not candidates for an ICD were randomly assigned to have an AED in their home or to control response (calling the emergency medical services and performing CPR; both groups were trained in this response) in case of a cardiac arrest. After ~3 years, there was no difference in survival between the groups.[119] AEDs were used in only 32 patients, of whom 14 received an appropriate shock and four survived to hospital discharge.[119] Thus, at present, home usage of AEDs is not recommended as a general health policy. However, there is no reason why a strategy of AED use in the home should not work, when there is a willingness to use these devices in the household of the individual at risk.

Conclusions

In the last 60 years much progress has been made in the understanding of the mechanisms, risk factors, and management of SCD. However, despite the progress in knowledge and the temporal reduction in cardiovascular mortality, SCD remains a major public-health problem. One of the challenges is determining the true incidence of SCD in the community, a problem that is exacerbated by the inconsistency of the definition of SCD used by investigators. Thus, consensus on a specific definition for SCD and establishing prospective, community-based surveillance programs using multiple sources to identify cases of SCD would enable more accurate determination of SCD incidence. In addition, a statement by the AHA published in 2008 recommended that all out-of-hospital cardiac arrests should be reportable events.[120]

Another challenge is the accurate identification of the person at risk. Virtually all individual SCD risk markers, including LV ejection fraction, lack specificity. Multimarker SCD risk scores that include demographic, clinical, and laboratory variables could prove to be more useful in identifying persons at risk of SCD. Several such risk scores have been developed and retrospectively tested among participants of large clinical trials,[56,57,61,62,75] but prospective testing in the general population has not been performed. Perhaps the greatest challenge in identifying the high-risk individual lies in the observation that SCD is the first manifestation of cardiac disease for the majority of those who suffer a sudden cardiac arrest. Heart disease surveillance programs and community-wide interventions for risk-factor reduction (for example, smoking cessation) are, therefore, extremely important in reducing the incidence of SCD. Indeed, a slower reduction in mortality from out-of-hospital SCD than for in-hospital SCD, and among those without known CHD

3-7

than in patients with CHD, suggest that there is room for improvement in the primary prevention of SCD. Finally, survival after sudden cardiac arrest continues to be dismal at ~5% and many individuals do not receive bystander CPR or timely defibrillation. Thus, educating the general public to perform CPR and use AEDs, and increasing their willingness and competence to do so, will be vital to increase survival after sudden cardiac arrest.

Review criteria

Articles were selected for inclusion in this Review by a search of the MEDLINE database. Key words used in the search were "sudden cardiac death", and "epidemiology" in combination with additional keywords (such as "genetics") relating to each subheading of the manuscript. The search was limited to English language articles and human data. No time limits were applied.

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3-8

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3-9

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3-10

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Electrocardiographic Findings in 122,043 Individuals

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MUCH OF THE KNOWLEDGE concerning electrocardiographic findings is based on information obtained from hospital and clinic populations. Less information has been obtained from healthy subjects. Hospital and clinic populations are preselected populations and introduce a degree of bias concerning the significance of observations made from them. Since a high percentage of patients admitted to a cardiac service do have underlying cardiovascular disease, many electrocardiographic findings appear to have a greater specificity in reference to diagnosis and prognosis because of their association with well-defined clinical events.

The United States Air Force began an electrocardiographic program for its flying personnel in 1957. This study required that an electrocardiogram be obtained on all subjects entering flying training and that an electrocardiogram be obtained on all individuals involved in flying duties. Prior to that time electrocardiograms were required only on men at the time of their fortieth birthday and each year thereafter or only when indicated for a clinical reason. The first 67,375 subjects studied during the first 2 years of the program are the basis of a previous report.[1-10] Since that time an additional 54,668 individuals have been studied. The incidence of electrocardiographic abnormalities occurring in the combined population of 122,043 individuals, as well as numerous electrocardiographic variations not previously reported, and the significance of such findings are the subject of this report.

Methods and Materials

The 122,043 individuals comprising the study are all male. Their ages range from 16 years of age to over 50. The population distribution by 5-year age groups is included in table 1. The vast majority of the population are flyers and must, of course, be in exceptionally good health to qualify for such duties. A large number of the younger subjects in the population are cadet applicants and presumably are in sufficiently good health to be considered for entry into a flying training program.

The age distribution of the population permits an analysis of the incidence of electrocardiographic findings as related to age. The incidence studies are based exclusively on the findings noted on an initial electrocardiogram. None of these abnormalities was detected as a result of a clinical event or a newly developed abnormality in the presence of a previous baseline normal record. Thus, the incidence studies are based exclusively on the electrocardiographic findings that might be found in an asymptomatic, apparently healthy population by means of an initial routine electrocardiogram. The major abnormalities have been expressed in rates per thousand for specific age groups when there were sufficient abnormalities present to permit such calculations. Electrocardiographic variations such as axis deviation, wave form configurations, and intervals that have not previously been reported were routinely tabulated in the last 54,668 individuals. These too have been expressed in rates per thousand per 5-year age group.

Clinical evaluations have been carried out in 955 cases and analyses of these findings are included in the study. These cases are in addition to those previously included in the publication on initial electrocardiographic findings.

Results and Discussion

There was a total of 5,773 electrocardiographic abnormalities noted in the group, for an incidence rate of 4.72 per cent. The incidence of the more frequent electrocardiographic abnormalities was calculated in terms of rate per thousand for each age group (table 2). Less common electrocardiographic abnormalities did not exist in sufficient number to permit realistic calculation on the basis of rate per thousand for specific age groups. The number of individuals with these types of abnormalities and the rate per thousand

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3-12

Table 1

Total Number of Persons in Each Age Group

Age group	Number of persons
16–19	7,072
20–24	37,159
25–29	21,681
30–34	12,966
35–39	22,028
40–44	18,359
45–49	2,044
50 and over	734
Total	122,043

for the entire population are given in table 3.

A total of 54,668 electrocardiograms has been analyzed for the presence of minor electrocardiographic variations not usually considered as electrocardiographic abnormalities or electrocardiographic diagnoses. Although none of these is thought to be of diagnostic importance, many show definite trends correlated with age. This analysis provides useful background data with which to interpret electrocardiograms at various age levels.

Atrial Rhythm

A total of 672 subjects presented with atrial rhythm. This interpretation was made in all those records that demonstrated a normal P-R interval with retrograde atrial excitation manifested by an inverted P wave in leads II, III, and aV_F. In such instances it is assumed that the primary pacemaker is located in the atria. A more detailed discussion providing a basis for this opinion has been previously reported.[2] This electrocardiographic pattern has been classified by other authorities as upper nodal rhythm with antegrade block and coronary sinus rhythm.[11, 12] In this study only two cases have been observed in which atrial rhythm was persistent.

Atrial rhythm commonly occurred during periods of sinus bradycardia when the rate of the sinus node falls below the inherent rate of the reserve atrial pacemaker. Atrial rhythm is easily abolished by atropine or sympathomimetic maneuvers, which increase the rate of the sinus node. Frequently, atrial pacemakers have a variable rate similar to the behavior of the sinus node. In the common variety noted in this survey, and classified as atrial rhythm, the upper range of the rate of the atrial pacemaker was less than 100 per minute. Rhythms initiated from an atrial focus at a rate more rapid than 100 beats per minute were classified as atrial tachycardia rather than atrial rhythm. The incidence of atrial rhythm in this population was 9.1 per thousand in the age group from 16 to 24 years, and 3.4 per thousand in all subjects 25 years of age or older.

Atrial rhythm is considered to be a benign variation in cardiac rhythm frequently associated with physiologic events that affect autonomic control of the cardiac rhythm. It is apparently in no way an indication of cardiac disease or significant abnormality in cardiac function.

Atrial Premature Contractions

Atrial premature contractions were noted in 534 subjects with an incidence rate of 4.3 per thousand. In nine subjects the prematurities were interpolated or true extrasystoles; 82 of the subjects had clinical evaluations. In none of the cases could significant evidence of underlying heart disease be demonstrated. Two subjects, during evaluations, demonstrated short bursts of atrial tachycardia, and two other subjects demonstrated numerous premature ventricular contractions after exercise, producing bigeminal rhythm in one case and multifocal prematurities in the other. There was no apparent significant difference in the incidence of atrial prematurities for the different 5-year age groups with the exception of men 50 years of age or over. The number of subjects in this age group, however, is quite small, and the rate per thousand for atrial prematurities is based on only seven subjects.

Atrial Flutter and Fibrillation

Only five subjects have been detected that present atrial flutter and fibrillation on their routine tracing recorded as part of this survey. Many other cases have been detected that have had previous normal survey tracings or have come to our attention for clinical

Table 2

*Most Frequent Major Abnormalities—Rates/1000**

Diagnosis	16-19	20-24	25-29	30-34	35-39	40-44	45-49	50 & over	Total	Rate per 1,000
Atrial rhythm	14.5 (103)	8.9 (332)	4.6 (101)	2.6 (34)	2.0 (45)	2.9 (54)	0.9 (2)	1.6 (1)	672	5.5
Atrial premature contractions	6.2 (44)	4.8 (181)	4.0 (87)	3.1 (41)	3.9 (86)	4.2 (78)	4.8 (10)	11.5 (7)	534	4.3
Nodal premature contractions	1.6 (12)	2.4 (90)	2.1 (53)	1.2 (16)	1.9 (42)	2.5 (47)	0.4 (1)	2.7 (2)	263	2.1
Ventricular premature contractions	4.6 (33)	6.2 (232)	5.7 (124)	8.3 (108)	8.2 (182)	11.8 (218)	19.0 (39)	21.7 (16)	952	7.8
First-degree AV block	6.0 (43)	7.4 (275)	6.2 (136)	5.0 (65)	5.9 (132)	7.1 (131)	4.8 (10)	13.6 (10)	802	6.5
Wolff-Parkinson-White	1.8 (13)	1.1 (54)	1.9 (42)	2.2 (29)	1.3 (30)	0.9 (17)	0.9 (2)	0 (0)	187	1.5
Right bundle-branch block	0.5 (4)	1.2 (48)	1.3 (29)	2.0 (27)	2.7 (60)	2.9 (54)	1.9 (4)	0.9 (7)	231	1.8
Intraventricular conduction defect	1.9 (14)	4.2 (159)	4.0 (87)	4.2 (55)	4.8 (107)	3.7 (68)	4.8 (10)	6.8 (5)	505	4.1
Ventricular fusion beats	0.4 (3)	0.2 (10)	0.5 (12)	0.6 (8)	0.4 (10)	0.5 (10)	0 (0)	2.7 (2)	55	0.7
Nonspecific T waves	15.1 (107)	9.9 (368)	10.4 (224)	8.9 (114)	12.1 (267)	14.4 (266)	18.1 (37)	29.9 (22)	1405	11.5
AV dissociation with AV nodal rhythm	3.1 (22)	1.3 (49)	0.37 (8)	0 (0)	0.09 (2)	0.17 (3)	0.5 (1)	0 (0)	85	0.7

*Numbers in parentheses are number of subjects.

reasons. Spontaneous atrial fibrillation in an asymptomatic population of this age group is quite common.

Nodal Premature Contractions

In 263 subjects nodal premature contractions were observed, resulting in an incidence of 2.1 per thousand subjects. There was no significant difference in the incidence rate for the different age groups. Forty-three subjects had extensive clinical evaluations, and no evidence of heart disease was detected in any of these individuals.

Nodal Rhythm

An interpretation of nodal rhythm was made in those records with retrograde atrial excitation and a P-R interval of less than 0.10 second or with retrograde atrial excitation occurring simultaneously with or following ventricular excitation. This does not include those cases diagnosed as atrioventricular dissociation but only those cases in which one pacemaker was responsible for excitation of both the atria and the ventricle, the atria being excited in retrograde fashion. This is usually an intermittent arrhythmia. True nodal rhythm meeting the above diagnostic criteria is a relatively uncommon arrhythmia in resting routine electrocardiograms. It was noted in only 18 subjects with an incidence of 0.14 per thousand. It occurs when the atrioventricular node functions as a reserve pacemaker and is more common in young individuals. Ten of the 18 subjects were 24 years of age or younger. No evidence of heart disease was detected in any of these subjects. Although true nodal rhythm is uncommon in a routine resting electrocardiogram, it is much more common during stress procedures involving breathing maneuvers, breath-holding, and orthostatic stresses. Its occurrence during maneuvers that increase vagotonia is not considered a significant abnormality.

One subject demonstrated nodal tachycardia. This diagnostic distinction was reserved for those cases with a nodal rate over 100 beats per minute. This subject is not included in the 18 examples of nodal rhythm.

Table 3

Less Frequent Major Abnormalities—Number of Cases

Diagnosis	16-19	20-24	25-29	30-34	35-39	40-44	45-49	50 & over	Total	Rate per 1,000
Atrial tachycardia		1	1	2					4	0.03
Atrial flutter		1							1	0.008
Atrial fibrillation		1	1		2		1		5	0.04
Nodal rhythm	1	9	3	1	4				18	0.14
Nodal tachycardia					1				1	0.008
Ventricular tachycardia		2		1	1	2			6	0.05
Second-degree AV block	2		1	1					4	0.03
Wenkebach phenomenon	1	3							4	0.03
Third-degree AV block	1	1	1						3	0.02
Left bundle-branch block			4		10	2	1		17	0.13
AV dissociation with idioventricular rhythm	1	2		3	2	3			11	0.09
Right ventricular hypertrophy					1				1	0.008
Left ventricular hypertrophy		2				3			5	0.04
Atrial hypertrophy			1		2	1	1		5	0.04
Myocardial infarction		5	1	9	15	5	4	3	42	0.34

Ventricular Premature Contractions

There were 952 (7.8 per thousand) subjects that had ventricular prematurities on the mounted routine 12-lead electrocardiogram (approximately 48 seconds of recording time). Ventricular prematurities, however, were a common finding in all age groups. The increased incidence of observed prematurities with increasing age suggests that the occurrence of some of the prematurities is secondary to changes accompanying aging. The common occurrence of prematurities, however, in all age groups makes it impossible, on an electrocardiographic basis alone, to determine whether the occurrence of ventricular prematurities is in fact secondary to significant cardiac changes. The frequency of prematurities in association with different age groups was also studied and expressed in rates per thousand (table 4). When so many different categories are involved, the groups are necessarily small, and definite conclusions cannot be drawn; however, the largest group of subjects (393) had from 2 to 4 ventricular premature contractions on a single record. It was evident that frequent ventricular prematurities (5 to 10 per record) were not uncommon. Frequent prematurities occurred in all age groups and no distinct differentiation on the basis of increased frequency of prematurities could be attributed to age. This suggests that although prematurities may be moderately frequent on the record, increased frequency alone is not an adequate basis to presume that their origin is secondary to cardiac disease.

Extensive evaluation of 238 subjects with ventricular prematurities was obtained. Only one of these subjects had clear-cut evidence of heart disease previously unknown and discovered only because an evaluation of premature ventricular contractions on a routine electrocardiogram was performed. A study of the influence of exercise and stress upon the occurrence of ventricular prematurities has been performed and will be the subject of a subsequent report.[13]

Of the 952 subjects only three examples of multifocal ventricular premature contractions were noted. Katz' criteria were used for classifying ventricular prematurities as multifocal in origin.[11] All three records demonstrated ventricular prematurities of dissimilar configuration with an inconstant relationship to the preceding beat. The dissimilar characteristic of the QRS complex was not due to the phenomenon of ventricular fusion. This points up the relatively uncommon occurrence

Table 4

*Frequency of Ventricular Premature Contractions in Different Age Groups**

Age Group	Group I 1 PVC	Group II 2-4 PVC's	Group III 5-10 PVC's	Group IV More than 10	Total
16–19	(2.1) 15	(2.2) 16	(0.8) 6	(1.1) 8	45
20–24	(1.8) 67	(2.6) 99	(1.1) 42	(0.4) 15	223
25–29	(1.6) 36	(2.5) 55	(1.3) 30	(0.5) 12	133
30–34	(3.8) 50	(3.3) 44	(1.5) 20	(0.9) 12	126
35–39	(2.5) 56	(2.8) 62	(1.4) 33	(0.9) 22	173
40–44	(3.0) 56	(5.1) 95	(1.3) 24	(0.9) 18	193
45–49	(6.8) 14	(7.8) 16	(2.4) 5	(1.9) 4	39
50–over	(8.1) 6	(8.1) 6	(10.8) 8	(0) 0	20
Total	(2.4) 300	(3.2) 393	(1.3) 168	(0.7) 91	952

*Numbers in parentheses are rates/1,000. Numbers not in parentheses are the number of subjects.

of true multifocal ventricular premature contractions in a routine resting electrocardiogram in an apparently healthy population.

There were 56 subjects with examples of interpolated prematurities or true ventricular extrasystoles.

Ventricular Fusion Prematurities

An additional group of 55 subjects demonstrated ventricular prematurities that had inconstant coupling with the preceding beat and demonstrated ventricular fusion beats. In many, but not all instances, a lowest common denominator for a ventricular pacemaker could be detected. One factor that made it impossible to ascertain this in all records was that a portion of the records had only a 46-second recording for a routine electrocardiogram. All these subjects appeared to be free of significant heart disease. Although many of these records could be classified as ventricular parasystole, at this time they are classified as ventricular fusion beats and a subsequent communication will deal more extensively with the problem of ventricular parasystole.

Ventricular Tachycardia

There were six examples of ventricular tachycardia. This interpretation was made when short bursts of three or more ventricular impulses occurred at a rapid rate. Three cases were studied and found to have heart disease. The other three were unavailable for evaluation. Ventricular tachycardia is a significant arrhythmia indicative of an irritable myocardium and is usually associated with some disease process.

Atrioventricular Block

An interpretation of first-degree atrioventricular (AV) block was made in all those records that had a P-R interval greater than 0.20 second. There were 802 (6.5 per thousand) subjects with this finding. There was no significant difference in the incidence rate for the different age groups except in those subjects 50 years of age or older. The latter age group was so small that it cannot be stated there was a true increase in incidence past the age of 50. Clinical evaluation on 111 cases of first-degree AV block, in addition to those previously reported, has been accomplished.[7] Of these, only four demonstrated evidence of heart disease; five of 139 previously reported evaluations had shown evidence of heart disease; six in the current study had a history of scarlet fever or rheumatic fever in childhood. The remainder had no history that would suggest the presence of a previous significant myocarditis or other evidence of heart disease. From an evaluation of individuals with first-degree AV block, it is our impression that the vast majority of these individuals, without other evidence of heart disease, exhibit this phenomenon as an individual variability of the refractory period at the AV junction as a physiologic mechanism. Special studies including hyperventila-

tion, orthostasis, exercise tolerance test, and intravenous injection of one-fiftieth grain of atropine produced shortening of the P-R interval to within normal limits in most subjects. A more extensive review of the influence of physiologic stresses and atropine on first-degree AV block has been reported previously.[7]

There were two cases that developed second-degree AV block with breath-holding maneuvers, and three showed the typical Wenckebach phenomenon during decreasing cardiac rate after exercise. The vagal slowing following termination of exercise appears to influence the AV node and increases its relative refractory period. The sensitivity of the AV node to vagal inhibition appears to be a major factor in producing first-degree AV block noted on routine electrocardiograms in a relative asymptomatic population.

Second- and third-degree AV block were very rare findings. There were only eight subjects with second-degree AV block on a baseline record. Of the new cases detected, none has had extensive evaluations, since they were applicants for flying training and were disqualified on the basis of this finding. Only three examples of third-degree or complete AV block have been noted. It should be emphasized that second-degree AV block may be induced in normal individuals with physiologic stresses despite the fact that its occurrence in baseline records in apparently healthy subjects is exceedingly rare.

AV Dissociation with Nodal Rhythm

Those instances in which the atria were stimulated by the sinus node and the ventricle was stimulated by the AV node in an intermittent fashion, were classified as AV dissociation with nodal rhythm. This phenomenon was noted in 85 (0.6 per thousand) subjects. The majority of these (71 subjects) examples were in individuals in the younger age groups. The cardiac rate was usually slow and dissociation was frequently induced when vagal inhibition slowed the sinus node below the inherent rate of the AV node, permitting AV dissociation to occur in a passive manner. AV dissociation may occur in younger individuals as a physiologic phenomenon unassociated with evidence of underlying heart disease.

Although AV dissociation is relatively uncommon on routine baseline records, it is a frequent and common occurrence during procedures of physiologic stress that influence vagal tone. AV dissociation may also occur when the AV node has an inherent rapid rate and may induce AV dissociation with nodal tachycardia. In these instances AV dissociation is not regarded as a benign phenomenon, and comprehensive evaluation of the subject is indicated.

Individuals who have a high degree of vagal control of cardiac activity are especially prone to demonstrate multiple complex arrhythmias without underlying heart disease. The capricious behavior of the AV junction is illustrated by the rapid transition in a normal subject from normal sinus rhythm to AV dissociation, recapture of the atria by the AV node, inducing transitory AV nodal rhythm followed by AV dissociation and recapture with the sinus node to induce normal sinus rhythm. AV dissociation and the complex arrhythmias related to it that may occur in healthy people do alter cardiovascular dynamics. Atrial contractions augmenting ventricular filling prior to ventricular systole may not occur in the proper sequence. AV dissociation may result in atrial contraction during the time that the ventricles are in systole. This alteration of the normal sequence of rhythmic atrial contraction followed by ventricular contraction appears to create no significant compromise of cardiac function during usual resting states.

AV dissociation in young healthy individuals disappears during exertion or other factors that induce cardiac acceleration. AV dissociation may accompany syncopal episodes induced by physiologic maneuvers and is one manifestation of the cardio-inhibitory phase of a syncopal response. This does not mean that AV dissociation in a healthy individual predisposes to syncope. It does mean that

Table 5

*Types of T-Wave Change**

Types	Number	Per cent	Rate/1,000
1. Low amplitude in all 12 leads	171	12.1	1.4
2. Low amplitude in limb leads	47	3.3	0.3
3. Low amplitude or inversion in precordial leads	63	4.4	0.5
4. Low amplitude in limb leads plus low amplitude or inversion in lateral precordial leads	429	30.5	3.5
5. Isolated T-wave inversion in precordial leads	56	3.9	0.4
6. Inverted right precordial leads	77	5.4	0.6
7. Wide QRS-T angle with leftward T vector and normal T amplitude	258	18.3	2.1
8. Wide QRS-T angle with leftward T vector and T-wave amplitude changes	333	23.7	2.7
9. Miscellaneous	20	1.4	0.2
Total	1454		

*Some patients had more than one type of T-wave change which explains the discrepancy between the total listed in this table and the 1,405 patients showing T-wave abnormalities. The per cent column does not add up to 100 per cent for the same reason, i.e., per cents were based on 1,405 persons with T-wave changes, not 1,454, which is the total frequency of types of T-wave change.

AV dissociation is one manifestation of the vagal events that are chiefly responsible for the mechanism of syncope commonly induced by physiologic maneuvers. Further compromise of cardiovascular dynamics by altering the normal sequence of atrial and ventricular contraction can contribute to the total picture of circulatory failure when it occurs as one feature of a syncopal episode.

AV Dissociation with Ventricular Rhythm

In the presence of AV dissociation the ventricles may be stimulated by a ventricular focus below the AV node. Cases that present this finding have been classified as AV dissociation with ventricular rhythm. All the cases classified in this group in this study are individuals with the rate for the ventricular pacemaker below 100 beats per minute. Commonly, the ventricular rate was 50 beats per minute or less. Obviously, AV dissociation with a ventricular pacemaker with a rate above 100 beats per minute is ventricular tachycardia. AV dissociation with ventricular rhythm behaves for the most part like AV dissociation with AV nodal rhythm. Periods of recapture and passive AV dissociation were noted. In the same individual, AV dissociation may be induced by premature firing of the ventricular pacemaker or it may be induced as a passive phenomenon. Five of these cases have been previously reported.[3] A total of 11 cases has now been observed. The additional cases show a pattern similar to those previously reported. The presence of such an arrhythmia is insufficient evidence to establish the diagnosis of heart disease without other findings. None of the individuals in this group has been demonstrated to have significant underlying heart disease. All of these subjects, by the classic definition of Kaufmann and Rothburger, could be considered as ventricular parasystole.[14]

Wolff-Parkinson-White Syndrome

Those records demonstrating a short P-R interval with definite evidence of pre-excitation were classified as Wolff-Parkinson-White syndrome. There were 187 (1.5 per thousand) subjects with this finding. There was no significant variation in the incidence rate for different age groups. This is to be ex-

Table 6

Frequency of Common Types of Nonspecific T-Wave Changes

T-wave changes	Number of subjects and rate per thousand by age group*											
	16-19		20-24		25-29		30-34		35-39		40 & over	
Low amplitude, all leads (less than 0.2 mv.)	0.71	(5)	0.60	(23)	1.06	(23)	1.77	(23)	2.40	(53)	2.03	(43)
Leftward rotation of T vector without amplitude changes	4.8	(34)	2.61	(97)	1.61	(35)	1.08	(14)	1.27	(28)	2.36	(50)
Leftward rotation of T vector associated with amplitude changes	2.96	(21)	2.26	(84)	2.99	(65)	2.54	(33)	0.72	(16)	2.36	(50)
Low T-wave amplitude in limb and lateral precordial leads	2.68	(19)	2.44	(91)	3.09	(67)	2.54	(33)	3.49	(77)	6.71	(142)
Inverted T waves in right precordial leads	1.41	(10)	0.81	(30)	0.41	(9)	0.61	(8)	0.27	(6)	0.66	(14)

*Rate per thousand in parentheses.

pected, since the entity is considered as a congenital variation. An additional 15 subjects have had extensive clinical evaluation in the new cases detected since the original 106 cases were reported.[4] There were no additional findings that would alter the original concept that the Wolff-Parkinson-White syndrome is a congenital variant and in itself is not indicative of underlying heart disease.

Complete Right Bundle-Branch Block

A diagnosis of complete right bundle-branch block was made in those subjects with a QRS duration of greater than 0.12 second and a broad S wave in lead I with a broad R or R′ wave in lead V_1. There were 231 (1.8 per thousand) subjects with this finding. Right bundle-branch block has been noted in all different age groups comprising the study. There was no significant difference in the incidence rate between the different age groups. None of the subjects in this group had previous normal electrocardiograms. A number of individuals with previous normal records have developed right bundle-branch block on subsequent tracings but are properly not included in the incidence figures of this report. It is our impression that right bundle-branch block may be detected at any age without evidence of significant underlying heart disease. Its occurrence in individuals past the age of 40, however, is more commonly associated with clinical findings suggestive of underlying cardiac disorder. Its occurrence in individuals with previously normal records is objective evidence of serial changes in the electrocardiogram and requires explanation.

The incidence rates in the different age groups noted in this study give strong support for the contention that complete right bundle-branch block may occur in the absence of underlying cardiac disease, despite the fact that its occurrence may also be induced in individuals with organic heart disease.

Complete Left Bundle-Branch Block

In 17 subjects complete left bundle-branch block was noted on the initial electrocardiogram. It is of interest that, despite the large population of 44,231 subjects below the age of 25, not a single instance of complete left bundle-branch block was noted. Apparently individuals with complete left bundle-branch block in the young age group usually have sufficient clinical evidence or history of heart disease that they are not considered for examination for entry into flying training programs. In view of the large population studies, it is unlikely that complete left bun-

dle-branch block occurs as an isolated asymptomatic congenital abnormality. The number of subjects with complete left bundle-branch block below the age of 35 is so small as to make incidence rates in this group unreliable. However, the incidence rate was 0.5 per 10,000 subjects below the age of 35, and 3.0 per 10,000 subjects 35 years of age and older. The apparent rarity of complete left bundle-branch block in healthy subjects below the age of 25 and its rare occurrence in subjects below the age of 35 clearly point up that left bundle-branch block in an asymptomatic population is commonly an acquired abnormality. Evaluation of cases presenting with left bundle-branch block in this laboratory has frequently shown evidence of underlying heart disease, including atherosclerotic heart disease and previous history of Bright's disease, scarlet fever, rheumatic fever, diphtheria, and other disease processes.

Intraventricular Conduction Defects

There are 505 subjects that had a QRS duration of 0.12 second with abnormal intraventricular conduction that could not be classified as right or left bundle-branch block or Wolff-Parkinson-White syndrome. The majority of these demonstrated terminal delay of the QRS complex. This group does not include instances of indeterminate QRS axis or abnormalities of the R to S ratio in V_1 or V_2. Very little clinical information is available in this group. Some of them may be the result of serial electrocardiographic changes and may represent unrecognized significant defects such as peri-infarction block, as described by Grant, and other conduction defects secondary to heart disease.[15] A large number of these subjects were in the younger age groups, and electrocardiographic variation was an incidental finding in an otherwise healthy subject. This point emphasizes the necessity for caution in attributing any important clinical significance to such a finding noted on a single routine electrocardiogram. If it can be documented to be a serial change, it then has considerably more clinical significance.

Table 7

Number of Persons with Inverted T_1 Found in 122,043 Subjects

Age group	Number of persons
16-19	1
20-24	4
25-29	0
30-34	3
35-39	5
40-44	15
45-49	1
50 and over	3
Total	32

Hypertrophy

There were no examples of left ventricular hypertrophy observed on routine electrocardiograms without antecedent history of cardiac disease. One reason for this is the exacting requirements for diagnosis of left ventricular hypertrophy used in this laboratory. Such interpretations are not made for increased QRS amplitude alone, marked left axis alone, or nonspecific T-wave changes occurring alone. An analysis of QRS amplitude in young healthy subjects has demonstrated that marked increases in QRS amplitude may occur in normal healthy people.[10] Similar statements may be made for left axis deviation and nonspecific T-wave changes. One example of right ventricular hypertrophy combined with atrial hypertrophy was detected as a result of a baseline routine electrocardiogram. Evaluation of this individual revealed previously undetected mitral stenosis with atrial hypertrophy and right ventricular hypertrophy. Mitral commissurotomy was subsequently performed. No other examples of hypertrophy problems were detected.

Nonspecific T-Wave Changes

An interpretation of nonspecific T-wave changes was made when specific variations in T-wave form from the usual normal electrocardiogram were observed. These abnormalities in T-wave amplitude or the direction of the T vector were classified into nine different types, as described in a previous publication.[8] The number of subjects in each category, and

the rate per thousand are listed in table 5. There were 1,405 (11.5 per thousand) subjects with nonspecific T-wave changes.

The five more common types of T-wave variations have been expressed on a rate-per-thousand basis for each age group in table 6.

True inversion of the T wave in lead I is uncommon in healthy asymptomatic individuals in routine records. Only 32 examples were noted in the entire population survey (table 7). Over half (19 subjects) of this group occurred in individuals 40 years of age or older.

Clinical data on an additional 314 subjects with nonspecific T-wave changes not previously reported have been evaluated; this information is summarized in table 8. In this survey over 65 per cent of the subjects presenting with nonspecific T-wave changes on a routine electrocardiogram had normal records when the tracings were obtained while the subject was in a resting and fasting state. Associated clinical evidence supporting the probability of underlying heart disease was noted in 11.4 per cent of the 314 subjects. Such evidence included elevated blood pressure over 140/90 mm. Hg, anginal symptoms, diabetes, cardiac enlargement on chest x-ray, and a very strong positive family history for heart disease. A clinical evaluation of the older subjects with the so-called juvenile pattern demonstrated that this group had the highest percentage of persistently abnormal records in the fasting state (60 per cent). This group also had the highest incidence of supportive evidence for underlying heart disease.

T-wave changes noted with increased heart rate after exercise or orthostasis indicate the influence of disturbance in the autonomic control of the cardiovascular system on the electrocardiogram. T-wave changes following glucose administration are apparently on a different basis and may be related to chemical changes occurring after carbohydrate ingestion. In individuals with T-wave lability, the type of T-wave change noted could frequently be induced by a variety of different methods.

The incidence rate of nonspecific T-wave changes in different age groups points up an increased frequency in younger subjects compatible with the concept that young individuals are more likely to have labile and inconsequential T-wave changes than subjects 35 years old and older. There was a stepwise increase in the incidence rate of nonspecific T-wave changes after age 35 years. This increased incidence rate with successively older age groups suggests the probability that the increased incidence is due to the type of cardiac abnormalities associated with increasing age.

It is important to emphasize that T-wave changes should be classified as nonspecific. In certain instances such changes are not innocuous and may represent significant underlying heart disease and in other instances they appear to be related to physiologic events and have no clinical consequence.[16] The distinction between T-wave changes due to heart disease from innocuous T-wave changes frequently cannot be made on the basis of an electrocardiogram alone and requires a comprehensive clinical evaluation.

Myocardial Infarction

There were 42 (0.34 per 1,000) individuals who had records compatible with myocardial infarction. The criteria for establishing this diagnosis have been published previously.[9] These criteria are as follows:

Inferior wall infarction: (1) Q_3 of at least 0.04 second in duration, and followed by an R wave; (2) Q in aV_F of at least 0.02 second in duration; (3) Q_2 must be present; (4) the amplitude of the QRS complex in lead III must be at least 5 mm. (0.5 mv.), unless Q_3 is greater than 2.5 mm. (0.25 mv.); (5) P_3 must be upright, and there must be an isoelectric interval between the P and Q waves.

Anterior wall infarction: (1) R waves must be absent in leads V_1, V_2, and V_3, *or* there must be a significant localized loss of R-wave amplitude in leads V_2, V_3, or V_4; and (2) P waves must be upright in lead V_2.

There were 12 individuals who had records compatible with anterior wall myocardial

Table 8

*Clinical Data on 314 Nonspecific T-Wave Subjects Studied**

Type of T-wave change	Fasting, normal	Fasting, abnormal	Other signs of cardiac disease	Positive family history of heart disease	Obese	Heart rate probably responsible for T changes	Orthostatic T changes demonstrated	Glucose tolerance test, T changes demonstrated	Total number studied
Low T amplitude in all 12 leads (< 0.2 mv.)	63 (24)	37 (15)	15 (6)	10 (4)	20 (8)	29 (7)	71 (17)	88 (21)	39
Low T amplitude in limb leads only (< 0.2)	64 (16)	36 (9)	12 (3)	24 (6)	20 (5)	24 (6)	81 (13)	81 (13)	25
Low T amplitude or inversion in lateral precordial leads only	73 (8)	27 (3)	27 (3)	0	45 (5)	0	50 (4)	75 (6)	11
Low T amplitude in limb leads + low amplitude or inversion in lateral precordial leads	64 (63)	36 (36)	14 (14)	21 (21)	13 (13)	37 (23)	71 (45)	81 (51)	99
Isolated precordial T wave changes	55 (6)	45 (5)	9 (1)	9 (1)	9 (1)	0	66 (4)	33 (2)	11
Inverted T waves in right precordial leads	40 (2)	60 (3)	20 (1)	0	0	50 (1)	0	50 (1)	5
A wide spatial QRS-T angle with T axis −30° or more	61 (44)	39 (28)	6 (4)	10 (7)	22 (16)	48 (21)	66 (29)	80 (35)	72
Wide spatial angle plus changes in T amplitude	81 (42)	19 (10)	8 (4)	27 (14)	25 (13)	33 (14)	74 (31)	90 (38)	52

*Numbers in parentheses are number of subjects.

infarction. Four of these were young men, aged 20 to 24 years. It is possible that the electrocardiographic pattern was associated with body stature and electrical axis. A precordial map from the second to the sixth intercostal spaces was obtained in each subject, and this interpretation was made only in those subjects who definitely met the criteria listed above and in whom the problem of electrode placement could be ruled out. There were two subjects who showed anterolateral myocardial infarction. There were 28 subjects that had records compatible with inferior wall myocardial infarction. Twenty-seven of this latter group were 30 years of age or older and 10 subjects were in the age group of 35 to 39 years. Not all had supporting clinical evidence of myocardial infarction. Subsequent tracings and follow-up data will lend greater significance to the importance of these electrocardiographic findings. Two subjects with tracings compatible with recent inferior wall myocardial infarction, upon interrogation, revealed a history within the month of myocardial infarction. The previous infarction would not have been detected in either of these subjects had it not been for the routine electrocardiograms recorded as part of this survey.

Sinus Rhythms

Sinus tachycardia was defined as a persistent heart rate over 100 and sinus bradycardia as a persistent heart rate under 60. The rate per thousand of both decreases with age for this population (table 9). The decreasing incidence of sinus bradycardia in the middle-age brackets is not unusual and corresponds to a loss of youthful vagal tone. Sinus tachycardia in the younger age groups is often caused by apprehension associated with the physical examination for flying training. For the purposes of this study sinus arrhythmia was diagnosed when inspection of the entire electrocardiogram elicited the subjective impression that marked rate variation in cyclic fashion was present. A prominent decrease in the rate per thousand incidence

Table 9

Miscellaneous Findings in 57,942 Subjects

Total number of persons Age group	5635 16-19 Number	 Per 1000	19,690 20-24 Number	 Per 1000	8080 25-29 Number	 Per 1000	2797 30-34 Number	 Per 1000
Sinus tachycardia	239	42.413	643	32.656	165	20.421	78	27.887
Sinus bradycardia	1388	246.318	5305	269.426	2040	252.475	625	223.454
Sinus arrhythmia	281	49.867	783	39.766	164	20.297	27	9.653
Sinus arrest	9	1.597	18	.914	2	.248	1	.358
Left axis deviation			118	5.993	57	7.054	25	8.938
Right axis deviation	12	2.130	23	1.168	10	1.238	2	.715
At limb lead QRS comp. 9 mm. or <	161	28.571	824	41.849	722	89.356	413	147.658
QRS amplitude 10 mm. or <	31	5.501	62	3.149	14	1.733		
$S_1 S_2$, SV_1	863	153.150	2683	136.262	1021	126.361	293	104.755
$S_1 S_2$, $R'V_1$	52	9.228	203	10.310	69	8.540	18	6.435
$S_1 S_2 S_3$, SV_1	1210	214.729	3574	181.513	1170	144.802	376	134.430
$S_1 S_2 S_3$, $R'V_1$	115	20.408	405	20.569	98	12.129	30	10.726
R' in V_1 and V_2 only	8	1.420	25	1.270	9	1.114	1	.358
R = or > S V_1	48	8.518	103	5.231	38	4.703	20	7.151
R = or > S V_2	204	36.202	819	41.595	421	52.104	165	58.992
Indeterminate QRS axis	56	9.938	210	10.665	73	9.035	28	10.011
Indeterminate QRS transition	2	.355	8	.406	5	.619	1	.358
Short P-R syndrome	107	18.988	331	16.811	104	12.871	35	12.513
All limb leads T waves 2 mm. or less	250	44.366	904	45.912	437	54.084	174	62.210
Notched P waves	263	46.673	1020	51.803	550	68.069	200	71.505

progressively with age coincides with previous medical opinion that sinus arrhythmia is a characteristic of youth.

Left Axis Deviation

Left axis deviation was defined as a QRS axis in the frontal plane greater than −30°. The incidence of this finding increased with age. A discussion of this phenomenon and the relation of left axis deviation to height, age, and weight is included in the former study.[10]

Right Axis Deviation

Only 66 subjects showed right axis deviation with a QRS axis in the frontal plane of +105° or greater. The majority of these were in the younger age group. In subjects 45 years of age or older no electrocardiograms were found with a QRS axis greater than +90° that were not associated with known heart disease.

Decreased QRS Amplitude

Low QRS amplitude was arbitrarily said to exist when all QRS complexes in the limb leads were 0.9 mv. or less. Measurements were made from the peak of the R wave to the nadir of the S wave as in the previous study of normal values. No special significance is attached to QRS complexes in limb leads 0.9 mv. or less; but this was merely chosen as a dividing line. All 57,668 electrocardiograms were judged according to those criteria. A definite increase in the rate per thousand with age was noted beginning with 28.5 per thousand in the youngest age group and terminating with 305.8 per thousand in the oldest age group. The even progression from one 5-year age group to the next is in conformity with the previously reported study based on QRS amplitude measurements calculated by a more refined method.[10]

3-23

6077 35-39		13,587 40-44		1582 45-49		409 50-54		85 55 & over		57,942 Totals	
Number	Per 1000	Number	Per 1000	Number	Per 1000	Number	Per 1000	Number	Per 1000	Number	Per 1000
187	30.772	405	29.808	67	42.351	14	34.230	2	23.529	1800	31.066
1148	188.909	2853	209.980	313	197.851	79	193.154	18	211.765	13768	237.617
39	6.418	71	5.226	9	5.689	3	7.335			1377	23.765
										30	.518
76	12.506	265	19.504	36	22.756	10	24.450	5	58.824	592	10.217
8	1.316	11	.810							66	1.139
1111	182.820	3009	221.462	401	253.477	115	281.174	26	305.882	6782	117.048
4	.658	6	.442							117	2.019
618	101.695	1377	101.347	122	77.118	29	70.905	4	47.059	7010	120.983
30	4.937	86	6.330	11	6.953					469	8.094
777	127.859	1770	130.272	196	123.894	40	97.800	10	117.647	9123	157.451
68	11.190	125	9.200	17	10.746	2	4.890			860	14.842
10	1.646	18	1.325							71	1.225
14	2.304	84	6.182	14	8.850	4	9.780			325	5.609
491	80.796	999	73.526	141	89.128	40	97.800	7	82.353	3287	56.730
55	9.051	115	8.464	11	6.953	5	12.225			553	9.544
4	.658	6	.442	1	.632					27	.466
90	14.810	180	13.248	25	15.803	7	17.115	2	23.529	881	15.205
445	73.227	1328	97.740	169	106.827	47	114.914	12	141.176	3766	64.996
492	80.961	1312	96.563	137	86.599	45	110.024	7	82.353	4026	69.483

S_1, S_2 and S_1, S_2, S_3 Patterns

An S wave in leads I and II or in leads I, II, and III indicates a terminal QRS force directed upward and to the right, probably as a result of delay in activation at the base of the heart. Whether an S wave or an R′ wave concludes the QRS complex in V_1 depends on the posterior or anterior direction of the terminal vector or upon the relation of the precordial electrode above or below the origin of the terminal vector. There is a steady decline of both the S_1, S_2 and S_1, S_2, S_3 pattern with age. Physiologic ventricular hypertrophy seen in the younger age groups may be responsible for this process. An alternative explanation is that progressive changes in the order of ventricular excitation with age result in eradication of terminal S waves in the standard limb leads.

R/S Ratio in V_1 and V_2

When the R-wave amplitude in V_1 or V_2 exceeded the corresponding S-wave amplitude, a notation was made and the statistics were assembled. The ratio in V_1 had a similar incidence for the various age groups. There was a progressive increase in the incidence of the R to S ratio in V_2 with age. An attempt was made to correlate the increase of left axis deviation with age to the increased incidence of a rightward transition zone with age. Only 35 of 54,668 individuals had both left axis deviation and rightward position of the transition zone; these were evenly distributed among the various age groups. It could not be concluded that left axis deviation and an early transition zone were related phenomena. Their simultaneous occurrence was not different from what chance would predict.

Indeterminate QRS Axis

Intraventricular conduction variation producing a QRS loop such that all limb leads were biphasic produced a manifest electrocardiogram for which the QRS axis in the frontal plane could not be determined. This occurred in 553 individuals; there was no significant variation between the age groups.

Short P-R Syndrome

The short P-R interval syndrome was defined as an absence of an isoelectric P-R segment in one or more standard limb leads associated with upright P wave and a short P-R interval (usually 0.10 second or less). There were 881 subjects with this finding. The incidence was approximately the same for all age groups.

Clinical correlation was not specifically sought for this electrocardiographic variation; however, since the vast majority of these subjects are asymptomatic and in apparent good health, it seems unlikely that heart disease, arrhythmia, or other medical problems would be a common associated factor for this population. Based on experience with this population, our opinion is that the short P-R interval syndrome is a normal variant due to accelerated AV conduction, which occurs as an individual idiosyncrasy corresponding to P-R interval prolongation at the other end of the scale. The possibility that the pacemaker is located in or about the AV node does not seem logical in view of the antegrade atrial excitation.

Low T-Wave Amplitude

A very frequent finding that was not considered a nonspecific T-wave abnormality was T-wave amplitude in all limb leads of 0.2 mv. or less. There was a steady increase in the frequency of this finding with each successive age group, independent of heart disease recognizable by currently accepted diagnostic criteria. Low QRS amplitude and low T-wave amplitude frequently occurred independently. A total of 6,782 subjects had low QRS amplitude, and 3,766 subjects had low T-wave amplitude. Only 586 subjects had both low QRS amplitude and low T-wave amplitude.

Notched P Waves

Marked notching of the P waves with an increased P-wave duration is usually ascribed to atrial disease and atrial hypertrophy. Minor degrees of notching of the P wave or dimpling is very frequent, however, and the incidence of this finding was calculated and is presented in table 9. The incidence appears to increase with age.

Summary

Electrocardiograms on 122,043 apparently healthy male subjects aged 16 years to over 50 years have been studied. Of this group 5,773 subjects (4.72 per cent) had electrocardiographic abnormalities. The more common abnormalities were expressed in terms of rate per thousand subjects for each 5-year age group. This provides a means of relating incidence to age. Each abnormality and its clinical significance is discussed.

In 54,668 subjects incidental findings such as notched P waves, amplitude, and wave forms were tabulated.

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Religio Medici

And if we should allow of the old Tradition that the World should last six thousand years, it could scarce have the name of old, since the first Man lived near a sixth part thereof, and seven Methusela's would exceed its whole duration. However to palliate the shortness of our Lives, and somewhat to compensate our brief term in this World, it's good to know as much as we can of it, and also so far as possibly in us lieth to hold such a Theory of times past, as though we had seen the same. He who hath thus considered the World, as also how therein things long past have been answered by things present, how matters in one Age have been acted over in another, and how *there is nothing new under the Sun,* may conceive himself in some manner to have lived from the beginning, and to be as old as the World; and if he should still live on, 'twould be but the same thing.—SIR THOMAS BROWNE. *Religio Medici.* Edited by W. A. Greenhill, M.D. London, MacMillan and Co., Ltd., 1950, p. 230.

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Interpretation of elevated postmortem serum concentrations of digoxin in infants and children.

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Abstract

The relationship between excessive postmortem digoxin concentrations (greater than 6.4 nmol/L) and administered dose, and antemortem levels and time of sampling after death were determined in 27 digitalized children who died in our hospital between March 24, 1981 and September 1, 1983. In all 27 cases, postmortem concentrations were higher than antemortem levels (9.5 +/- 2.5 nmol/L and 3.12 +/- 1.72 nmol/L, respectively). In none of these patients was there clinical or electrocardiographic evidence of digitalis toxicity. There was a significant correlation between antemortem and postmortem determinations, and between time of sampling after death and postmortem concentration. Positive correlation existed between antemortem or postmortem concentrations and dose per kilogram. The degree of elevation in digoxin levels was uniform in most cases, and the likelihood of elevation falling in the range 3.5 to 7.0 nmol/L was 66%. If the estimated concentration of digoxin at the time of death was taken as baseline, in 75% of cases the subsequent elevation was between 5.3 and 8.3 nmol/L (mean, 6.5 +/- 1.1 nmol/L). Digoxin concentrations measured in newborn infants not receiving digoxin were significantly higher after death (1.5 +/- 0.3 nmol/L) than in age-matched living infants not receiving digoxin (0.5 +/- 0.3 nmol/L). These data indicate that the size of antemortem dose, the time of sampling after death, and existence of endogenous digoxinlike factors affect postmortem readings of digoxin levels. Consequently, excessive postmortem determinations cannot be directly interpreted as proof of toxic antemortem levels.

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3-27

Therapeutic Drug Monitoring
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Postmortem Drug Analysis: Analytical and Toxicological Aspects

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Summary: Publications focusing on the analysis of postmortem specimens for the presence of drugs were reviewed with particular reference to systematic toxicological analysis. Specimens included blood, liver, other solid specimens, and fly larvae. Extraction techniques published during the past 10 years most commonly used traditional solvent extraction techniques. High-performance liquid chromatography coupled to multichannel wavelength detection was most commonly used, which would easily lend itself to liquid chromatography-mass spectrometry. There were few practical differences in the assays validated for a range of postmortem specimens to those in other forms of forensic toxicology, unless substantially decomposed tissue was used. When putrefied specimens were analyzed, a back-extraction or other form of specimen cleanup was recommended to reduce interfering substances. Many immunoassays designed for urine have been adapted for use in blood and tissue homogenates. Immunoassays designed for blood analysis, however, are likely to have more useful cutoff values than immunoassays optimized for urine testing. Postmortem specimens provide less stability for a number of drugs than other types of specimens. This is particularly a problem for cocaine, heroin, and some antidepressants, antipsychotics, and benzodiazepines. A number of artifacts occur postmortem, which affects the concentration of drug in specimens. This includes postmortem redistribution for drugs with a high tissue concentration relative to blood. Consequently, the likely extent of any change in concentration is relevant to the interpretation of doses and drug effects.
Key Words: Review—Systematic toxicological analysis—Postmortem toxicology—Drug stability—Redistribution.

The detection of drugs and poisons in postmortem specimens can pose a special difficulty compared with clinically derived specimens. The presence of putrefactive compounds and the often-altered (decomposed) nature of specimens limit the direct applicability of clinically validated assays in a postmortem setting. In addition, several alternative specimens can be collected in a postmortem setting. These may include liver, muscle, fat, lung, brain, bone, pleural effusions, and even larvae of insects feeding on the host.

The development of an efficient and extensive drug screening procedure is as important for forensic cases as it is for clinical cases and forms the basis for either excluding the involvement of drugs and poisons in a case, or detecting such substances when they are present. A review of the use of systematic toxicological analysis (STA) in clinical and forensic cases has been published recently (1). A review of gas chromatography-mass spectrometry (GC-MS) procedures for STA is available and has generally focused on the determination of drugs of abuse in blood (2,3). A review of high-performance liquid chromatography (HPLC) techniques using photodiode array detection (DAD) is also available (4). The advantages of HPLC coupled to DAD are also reviewed by Lambert et al (5), and Hoja et al (6) have reviewed the use of HPLC coupled to MS.

When determining the concentration of drug in biologic matrices, it is important to know the stability of the substance in such tissues. This situation is relevant no more so than in forensic toxicology, where tissues are

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likely to be exposed to the elements for prolonged periods. The extent of chemical change in the postmortem interval, or even metabolism occurring postmortem, may affect the interpretation of results. Some drugs are known for their unstable nature. For example, nitrobenzodiazepines are actively converted to their respective metabolites by bacteria in the postmortem interval (7). Consequently, flunitrazepam is rarely confirmed positive in blood specimens taken at autopsy. Cocaine has also been subject to postmortem breakdown to its metabolite, benzoylecgonine (8,9).

This manuscript focuses on the analysis of blood and other postmortem specimens that are not traditionally used in clinical toxicology, reviews published papers focused on the systematic screening of postmortem specimens, and describes analytical features and artifacts associated with the analysis of postmortem specimens.

MATERIALS AND METHODS

Refereed analytical articles written in English were searched using the National Library of Medicine's PubMed MedLine database from January 1990 to December 2000 using "postmortem drug analysis" as the search string. Methods cited from these references or other methods available to the author were also included that discussed or presented methods that presented broad class screening systems and the use of alternative specimens unique to postmortem toxicology. To limit the scope of this review, this paper is restricted to illicit drugs and drugs approved for therapeutic use by regulatory authorities, unless poisons are related to known drugs. In addition, urine-based toxicological techniques were not reviewed unless of special significance, because urinalysis methods are subject to many recent reviews. A general review on postmortem drug stability and other artifacts was provided based on published literature.

RESULTS

Specimens Used

The choice of specimen is often dictated by the case being investigated, but the most common specimens used for the screening of drugs in postmortem cases are blood, liver, and urine. Postmortem blood presents problems in most methods validated for plasma or serum due to its higher viscosity and often variable condition.

Urine is frequently used as a screening specimen, but it is not always available. Its preparation has been reviewed elsewhere (1).

Liver is the most frequent specimen used in postmortem toxicological analysis. In addition, vitreous humor, bile, brain, and lung are also used in certain types of analyses. Pleural effusions (10), muscle (11–16), fat (13), and bone (13,17,18) have also been used by toxicologists in special types of analyses. Hair analysis has also been used to provide evidence of longer-term exposure (or abstinence) of drugs (19–24). Larvae (maggots) found in putrefying bodies can be used to obtain evidence of the presence of drug in human remains (15,25–29).

A list of recommended specimens for common case types in postmortem forensic toxicology is shown in Table 1. Details of some of the specimens are reviewed below.

Liver

The liver has been a primary solid tissue for use in postmortem toxicology, and often the drug test results in this tissue supplement any blood toxicology data. Because some drug diffusion is possible from the small bowel, the use of tissue from deep within the right lobe is preferred (30).

Various analytical methods are published and include simple homogenization of tissue in water and/or treatment with the enzyme subtilisin to improve recoveries caused by precipitation of homogenized tissue with ethanol or acetone (to remove proteins) before extraction (10,31–38).

Bile

Bile is a useful fluid for detection of a number of drugs and can even be used as a screening fluid when urine is not available. This fluid contains relatively high concentrations of morphine, benzodiazepines, and colchicine. Because it contains high concentrations of bile acids and

TABLE 1. *Recommended specimens collected in postmortem cases*

Type of case	Specimens collected
Suicides, motor vehicle crashes, and industrial accidents	Blood, urine, vitreous humour, liver
Homicides and suspicious cases	Blood, urine, vitreous humour, liver, bile
Drug-related cases	Blood, urine, vitreous humour, gastric contents, bile, liver
Volatile substance abuse cases	Blood, urine, vitreous humour, lung fluid or tied-off lung, liver
Heavy metal poisoning and exposure to other poisons	Blood, urine, vitreous humour, liver, hair, kidney

other endogenous substances, bile analysis requires specific extraction techniques to isolate any drugs and to prevent interference (39). Because drug concentrations are often higher in bile than corresponding blood specimens, the use of a smaller sample volume and dilution into a buffer is recommended, together with a cleanup step.

Vitreous Humor

Vitreous humor is also a useful fluid to screen for a range of drugs, as well as a number of biochemical markers (40). The vitreous humor is essentially a salt solution with very little protein; hence, drugs present can be extracted as though they were solutions in a buffer. Vitreous humor is commonly analyzed for ethyl alcohol content to supplement blood alcohol concentrations, particularly to exclude putrefactive formation of alcohol and contamination of blood from other fluids.

Muscle and Fat

These tissues are not analyzed frequently due to the difficulty in reliably extracting drugs and because of substantial variability in drug/metabolite concentrations from one site to another (11,12). However, these tissues represent the greater mass of a body and represent a greater body burden of drug than any other tissue mass. These tissues should be finely minced and homogenized until a homogeneous suspension is obtained (11). The use of an enzyme digestion procedure similar to liver can improve the extractability of drugs (13). A cleanup extraction step for basic drugs, such as re-extraction into an acidic phase and a third extraction into solvent from basic pH, reduces any significant interferences.

Bone and Bone Marrow

Bone can be removed from many locations in a body; use is constrained more by practical issues such as availability of bones in skeletal remains. There are no data to suggest that one anatomic region is better than another; however, large bones such as the femur are certainly easier to work with than smaller bones. Bones should be cut into small segments (e.g., femur rings) or crushed (13,17,18). Bone marrow can be diluted and extracted as for fluids, unless residual marrow is treated with methanol (17,18).

Pleural Effusion

Fluids contained within the pleural cavity develop during the process of putrefaction. This effusion, which arises from liquefaction of tissues, has been used as an alternative specimen for drug detection (10). The use of a basic drug extraction with acid back-extraction was sufficient to allow detection of drugs using conventional GC with nitrogen phosphorus detection (NPD) or MS.

Hair and Nails

Hair specimens have been used to test for exposure over weeks to months to heavy metals and drugs. The target analytes in hair are predominantly the parent drugs such as amphetamines, cocaine, delta-9-tetrahydrocannabinol (THC), and heroin and 6-acetylmorphine (6-AM) for heroin. Hair is usually taken from the back of the head (23). A number of factors affect the uptake and retention of drugs in hair (41).

Finger and toenails can also be taken and subjected to drug analysis (42,43). This provides an even longer potential window of exposure than hair. However, relatively little is known about the mechanisms of uptake and retention, so interpretation is more difficult.

Immunoassay Screening Techniques

Immunoassay screening techniques used in clinical toxicology can be used in postmortem toxicology, particularly when urine is available. Urine obtained in cases when significant putrefaction has occurred can lead to false-negative results. These can be reduced by the use of urine treated with methanol before an enzyme multiplied immunoassay technique (EMIT) drugs of abuse screen. False-positive results are also common for the amphetamine and stimulant class of drugs. This occurs due to the presence of amine putrefaction products. Postmortem urine specimens from cases with proteinuria and lactic aciduria will also give false-positive screening results due to the presence of lactate dehydrogenase, lactic acid, and protein (primarily albumin) (44).

When urine is not available, immunoassays designed for blood and other tissues need to be used, or alternatively urine-based kits may be adapted and validated for alternative specimens.

Other biologic specimens such as bile and liver homogenates can be screened using immunoassay kits. Prior treatment with a solvent or precipitation of proteins is required before analysis of these specimens. Precipitation of tissue homogenates with 2 volumes of methanol gave few false-positive screening results for opioids, cannabinoids, and diazepam, although 9% of postmortem samples were falsely positive for amphetamines in postmortem blood (45). There was insufficient analytical sensitivity for high-potency benzodiazepine detection.

This technique had been applied previously with EMIT assays using methanol (46,47), or acetone to precipitate proteins before analysis (48).

The acetone precipitation method (3 volumes) was found to give superior detection for the five drugs of abuse classes using fluorescent polarization immunoassay (FPIA) than EMIT, particularly for cannabinoids and decomposed blood specimens (49). Dimethylformamide has also been used successfully to treat postmortem blood (2 volumes) before EMIT analysis for amphetamines, barbiturates, methadone, methaqualone, PCP, and propoxyphene (50).

Solvent extraction provides the highest sensitivity and reduces interference from other components in the specimen. Radioimmunoassays (RIAs) designed for blood tend to have better sensitivity than kits designed for urine and adapted for blood. A coated-tube RIA was found to have improved cutoff values compared with a double antibody RIA for the detection of drugs of abuse in postmortem blood (51).

The use of microplate enzyme immunoassay for the detection of drugs (e.g., enzyme-linked immunosorbent assays) is a quick and convenient method for the analysis of drugs in blood and even tissue homogenates. This technique has been shown to achieve sensitivities and specificities comparable to RIA and has the advantage of automation (52,53). This technique is also used in hair analysis of drugs (54,55). Analytic cutoff values vary between manufacturers and batches of antibodies and the degree of dilution used.

Extraction Techniques and Chromatography

Extraction procedures used in the papers forming part of this review used either liquid-liquid or solid-phase (SPE) procedures for the analysis of acidic, neutral, and basic drugs (Table 2).

There is little to differentiate solvents used in various methods with respect to their extraction efficiency and selectivity for drug extraction; they are similar to those used in clinical toxicology for blood, serum, or plasma analysis (1). The use of a single-step extraction from basic pH will recover a range of basic and neutral drugs. This has been the traditional method for isolating drugs from biologic specimens and is still widely used in forensic laboratories conducting toxicological testing on postmortem blood.

Direct precipitation with acetonitrile has also been used in conjunction with HPLC and DAD detection, although sensitivity is less than in procedures involving concentration steps. Direct precipitation with a solvent is mainly directed toward analysis of acidic drugs (56). The use of ammonium chloride salting-out with ethyl acetate followed by a wash step with hexane appears to be an effective means to extract a range of acidic drugs in postmortem blood and other tissues (57).

Methods published in this period on the measurement of acidic drugs varied substantially in their approach. The use of saturated ammonium chloride and ethyl acetate is an efficient way to extract weakly acidic drugs from blood (58). Dichloromethane/propan-2-ol extraction at pH 4.6, or after acid hydrolysis, has also been used to detect acidic drugs (59). Direct precipitation is a quick and effective method for such drugs when using HPLC as the analysis tool (56).

An extraction pH lower than 5.0 is required to isolate the carboxyl-containing drugs such as the nonsteroidal anti-inflammatory drugs unless forcing conditions are used, such as saturated ammonium chloride solution with a strong solvent such as ethyl acetate (1).

When liver is used as matrix, more sophisticated extraction schema are needed (31,60). Enzyme digestion of liver under basic pH has been advocated to release protein-bound drug before extraction (31,38), although multiple extraction of lyophilized liver has been successful for HPLC screening. A cleanup extraction is recommended when using liquid-liquid extraction on liver homogenates or when blood is significantly putrefied (61). This may include re-extraction of the solvent into a small volume of dilute mineral acid followed by basification and extraction into the original solvent.

An efficient SPE technique has also been published using liver homogenates (31). Ion-exchange resins have been successfully used for acidic drugs in postmortem blood and other biologic fluids (39). SPE techniques have been reviewed for general toxicological work (36, 62,63). The review by Scheurer and Moore (36) also provides methods for a number of postmortem specimens, including brain, liver, intestine, kidney, muscle, bone, fat, and meconium. Both Bond Elut Certify and Clean Screen SPE columns have been shown to be acceptable for routine drug screening in STA (64).

Benzodiazepines were the focus of several papers on postmortem drug analysis in this review period (34,60,65–67). Their inclusion in STA is important because they are a major group of drugs and are not extracted in the basic/neutral group if a conventional acid back-extraction is used (34,65–67). The 7-amino metabolites of flunitrazepam, clonazepam, and nitrazepam are the most difficult to detect in postmortem specimens. Procedures for this class of drugs have been reviewed generally for toxicological applications (1,68).

The application of traditional analytical extraction techniques to bone assumes a special level of difficulty,

3-31

TABLE 2. *Summary of recent published screening methods for postmortem specimens*

Reference*	Tissue	Drug classes	Extraction method	Conditions	Comments
58	Blood	Weakly acidic and neutral drugs	Blood (1 mL) was treated with saturated ammonium chloride and extracted with ethyl acetate. Extract was evaporated to dryness and residue reconstituted.	25-m NB-54 and NB-1701 columns, 0.32 mm ID with 0.1 µm film, splitless injection on GC-NPD, gradient to 280°C.	Validated for barbiturates and benzodiazepines and a number of basic drugs. Uses automated drug identification with Micman™ software.
82	Blood	Basic and neutral drugs	Blood (0.2 mL) was diluted with 0.7 mL water and extracted with 0.1 mL ammonia and diethyl ether. The ether was evaporated and the residue reconstituted with methanol.	Various FSC and analyzed by GC-thermionic detector, EI MS; and also on HPLC Speri-5 RP-18 100 mm × 4.6 mm ID using methanol/water (70:30), detection at 228 mm	Validated for several drugs, can also be used for liver homogenates
61	Blood	Basic drugs	Blood (2 mL) extracted with toluene and ammonia solution; followed by back-extraction into 0.4 mol/L sulfuric acid (toluene layer used later) and re-extracted from alkalinized acid into toluene (fraction A). Re-extraction of original toluene layer into 6 mol/L HCl was used for benzodiazepines.	Isocratic HPLC-DAD on two columns: APEX ODS, 5 µm 25 cm × 4.6 mm ID and Water µPhenyl, 5 µm, 15 cm × 3.9 mm ID using ACN/0.25% phosphoric acid/TEA pH 3.4 (25:10:5) and ACN/0.025% phosphoric acid (50:50)	Over 100 drugs detected in 15 min, including benzodiazepines
56	Blood	Broad class screening	Direct precipitation with acetonitrile	HPLC-DAD using Spherisorb S5 ODS-2, 5 µm, 100 mm × 3.8 mm ID, gradient elution 10–60% acetonitrile in pH 3.1 phosphate buffer	Detects over 120 drugs and metabolites including analgesics, anti-inflammatories, anti-convulsants, antidiabetics, barbiturates, theophylline, some benzodiazepines & diuretics, herbicides, etc.
78	Blood	Basic/neutral drugs	Blood (1 mL) extracted with butyl chloride after 2 mol/L Tris, pH 9.2 buffer	12-m BP-5 0.53 mm ID, 1.0 µm film, splitless mode, gradient to 310°C, detection by NPD; run time 40 min	Benzodiazepines and barbiturates detected with a range of basic drugs
59	Blood and liver	Acidic, neutral, and basic drugs	Tissue (1 mL) was treated either with acetate buffer (pH 4.6) and extracted with diethyl ether (A), or treated with borate buffer (pH 8.5) and extracted with DCM/isopropanol (9:1) (B), or treated with 2 mol/L HCl, heated for 30 min at 100°C, basified and extracted with DCM/isopropanol (9:1) (C).	HPLC-DAD using Superspher RP-18 column (125 mm × 4 mm ID), gradient elution with ACN/TEAP pH 3.0 (0–70%).	Authors identified endogenous substances in alkaline blood and liver extracts. Drugs identified by RI values and UV spectra.
39	Blood	Acidic drugs and others	Blood (1–2 mL) diluted with pH 2.4 buffer and treatment with XAD-2 resin. Following washing steps drugs were extracted with isopropyl ether.	HPLC-DAD using a variety of columns and solvent conditions	Provides extensive validation for acidic, neutral, and basic drugs and a large library of retention times on reversed-phase columns
35	Blood, tissue homogenates, stomach	Basic drugs	Tissue (1 mL) is extracted with 1-hexane-ethyl acetate (7:3) at pH 9.5. Solvent is evaporated and extract is applied to column.	HPLC-DAD using Aluspher RP-select B column (125 mm × 4 mm i.d., 5 µm particle size). Gradient solvent was 0.0125 mol/L NaOH in methanol (10–90%)	Over 130 basic drugs listed with capacity factors

3-32

TABLE 2—(*Continued*)

Reference*	Tissue	Drug classes	Extraction method	Conditions	Comments
33	Blood, tissue homogenates, urine	Basic, neutral, and acidic drugs	Blood or tissue treated with KCl & pH 8 phosphate buffer, extracted with butanol-ethyl acetate (1:5)	Multicolumn REMEDi HS (BioRad), chromatographic conditions not given, multiple wavelength UV detection	Library of over 500 drugs and metabolites, semiautomated drug identification system, broad class screening. Tissue homogenates prepared in water.
31	Liver	Acidic, neutral, and basic drugs	Enzyme digestion of 0.4 mL sonicated liver homogenate (subtilisin Carlsberg, pH 10.5) and Bond-Elut Certify SPE, 2 fractions: acetone-chloroform (supernatant) and ethyl acetate-ammonia (pellet)	GC-FID & NPD, 30-m HP-1 0.53 mm i.d., film 0.88 μm, gradient to 285°C	Validated for a large range of drugs and liver amounts, with extraction yields
57	Blood	Acidic and neutral drugs	Blood (1 mL) is treated with saturated NH_4Cl solution and extracted with ethyl acetate. Solvent is evaporated and extract reconstituted into ACN, which is washed with ACN-saturated hexane. The ACN layer is applied to chromatography.	HPLC-DAD using microbore ODS-Hypersil (200 mm × 2.1 mm ID, 5 μm particle size) and ACN/phosphate pH 3.2 gradient (5–50%) GC-FID using HP-5 column (25 m × 0.25 mm ID, 0.33 μm film) at 100–310°C temperature program	Uses HPLC and GC to detect a range of acidic and neutral drugs. No derivatization is used for acidic drugs on GC.

ACN, acetonitrile; DAD, diode-array detector; DCM, dichloromethane; EI, enzyme immunoassay; FSC, fused silica column; FID, flame ionization detector; GC, gas chromatography; HPLC, high-performance liquid chromatography; MS, mass spectrometry; NPD, nitrogen phosphorous detector; ODS, octadecylsilane; TEAP, triethylamine phosphate.

because this tissue is not readily broken down or homogenized. It is recommended to grind or slice the tissue into small pieces and to extract out drug with prolonged contact with solvents (13,17,18). Fluid bone marrow can be diluted with buffer and treated as a viscous fluid. Dried bone marrow, however, is extracted similar to bone (by prolonged contact with a solvent such as methanol). Once an extract is obtained, conventional analytical techniques can be applied (e.g., GC-MS or HPLC). Because analytical recovery cannot be reliably estimated and drug content in bone is less likely to reflect recent exposure, tissue concentrations can only be used qualitatively.

The extraction of drugs from larvae usually involves homogenization of the tissue and extraction by conventional techniques used for other tissues. Larvae are first homogenized in water or dilute buffer (15,26,69), although proteins can be precipitated out with sodium tungstate before solvent extraction (25). Morphine and other opiates have been detected by RIA (26,70) or by FPIA (29) from a direct homogenate of larvae. Conventional analysis can be conducted on extracts using either HPLC or GC (25–29,69,71).

A number of extraction methods for hair have been published (23). The choice of method depends on the drug chosen, because some methods will degrade certain drugs (e.g., sodium hydroxide digestion will degrade drugs sensitive to strong base (20)). Benzodiazepines, cocaine, and heroin are notable examples that require less caustic conditions. Extraction with warm methanol or other solvents such as dichloromethane protect these labile drugs, although the recovery may be lower (21,24, 72,73). In some cases, hair is ball-milled into a fine powder and the drugs are extracted with methanol. This approach, however, can cause problems with loss of fine hair powder from air movements.

Chromatographic detection is frequently based on HPLC UV or DAD using either retention indices or matching algorithms (5,39,56,59,60,74–77). The HPLC methods included procedures directed toward acidic/neutral (39,57), basic/neutral (61,78), or all drug classes (33,56,59). All published studies used photodiode array or multiple wavelength detectors, and most used octadecyl-bonded columns. LC-MS is an emerging technique that combines the separation power of HPLC with the specificity of MS (6,79,80). The use of semi-micro columns can lead to reduced run times without sacrificing selectivity and sensitivity, and importantly provides an ability to interface more easily with MS (81).

The GC-based procedures for general drugs used either a flame ionization detector (31,57) or NPD (31,58, 78,82), although all would be capable of interfacing with an MS, if desired. All used fused silica columns of low to moderate polarity with either narrow- to medium-bore columns. As with most clinical toxicological screening

systems, drugs were generally analyzed without chemical derivatization.

Multiple chromatographic and/or detection systems were used by seven of the cited papers (31,33,39,57,58, 61,82). The use of multiple columns was most popular for both HPLC and GC systems, although the use of two detectors (31) or the use of both GC and HPLC (57,82) would give an inherently greater coverage of possible drugs than one chromatographic system alone. A further refinement used in our laboratory is the splitting of the effluent from a GC column into both an NPD and MS. Rasanen et al (66) used dual-column GC and electron capture detector on t-butyldimethylsilyl derivatives of benzodiazepines with confirmation on MS; however, the 7-amino metabolites were not detected with sufficient sensitivity with these derivatives.

Stability and Artifacts

Postmortem specimens, more so than any other specimen, are likely to show some form of altered state because of either an extended postmortem period before collection or inadequate or prolonged storage before analysis. Liquefaction of tissues occurs during extended postmortem periods and together with fluid specimens contains more endogenous substances likely to interfere with analytical systems, even with GC-MS procedures. This is further exemplified by the analysis of insect larvae that are likely to contain drugs originally present in the host body.

Stability of Drugs in the Postmortem Period

Some benzodiazepines, particularly the nitrobenzodiazepines (nitrazepam, flunitrazepam, and clonazepam), are subject to postmortem change (7). Postmortem specimens collected for nitrobenzodiazepine determination should be analyzed as soon as possible to minimize the loss of their respective 7-amino-metabolites. Other benzodiazepines are also subject to postmortem change, but these changes can be minimized if specimens are stored at –20°C or lower and analyzed promptly (83).

The stability of other drugs of abuse has been investigated (8,84–89). Blood specimens containing cocaine and benzoylecgonine show poor stability and need to be analyzed within a reasonable time period for reliable interpretation (85). Dugan et al (90) showed that cocaine concentrations in urine can change by as much as –37% over a 12-month period when stored at –20°C. Others have shown under the same conditions that cocaine and benzoylecgonine are stable for up to 6 months (86,87).

The acid metabolite of THC, 11-nor-9-carboxy delta-9-tetrahydrocannabinol (carboxy-THC), shows significant losses in concentration not only when urine is stored at room temperature for several days but also after long-term frozen storage (87–89).

6-AM is relatively labile in urine at room temperature, undergoing deacetylation to morphine (91). After freezing for 12 months, 6-AM showed less than a 2% loss. No appreciable loss of 6-AM over the short term would be expected (3 months) if specimens were frozen (92). Deconjugation of morphine metabolites to morphine has been observed in liver (8). Morphine is relatively stable in specimens when stored frozen but shows significant losses when stored at 4°C or higher for more than a few days (93).

Chlorpromazine has been found to be unstable in postmortem specimens stored for prolonged periods (94,95). Similar results have been found for thioridazine (95).

Redistribution

The process of redistribution can affect the concentration of all analytes in postmortem blood as a result of a disruption of cellular membranes, causing alterations of drug concentrations within tissue elements and diffusion from one tissue to another. This process is particularly significant for drugs with high lipid solubility or high tissue concentrations relative to blood. Changes in concentration up to 10-fold in cardiac blood are known when compared with specimens taken antemortem or shortly after death. The drugs most affected include digoxin (96,97), propoxyphene (98,99), and tricyclic antidepressants (98–100).

Changes have also been reported for methadone (101,102), fluoxetine (103), and methamphetamine/amphetamine (104–106). In humans, morphine appears to be little affected (107,108).

Femoral blood is also subject to redistribution after death, although less so than cardiac or centrally collected blood. Postmortem drug redistribution processes are not limited to blood. Liver and lung tissue show differences in the concentration of drugs, depending on the nature of the drug and whether diffusion of drug has occurred from neighboring tissues or the blood supply. For example, the left lobe of the liver is more likely to exhibit elevated drug concentrations than the right lobe (30).

DISCUSSION

The analysis of postmortem specimens can provide special challenges for forensic toxicologists when they

receive solid tissues, or if the specimens have been obtained from substantially decomposed bodies. With the exception of these situations, a review of the screening techniques published in the past decade suggests that they are almost identical to screening techniques published for blood obtained from live subjects (1). HPLC is a common analytical system used in postmortem toxicology, although it not clear whether this necessarily reflects worldwide use of HPLC compared with GC with GC-MS in forensic toxicology. The widespread use of HPLC, its flexibility with respect to separation of a large range of underivatized substances, and the possibility of confirmation by LC-MS demonstrate its importance in forensic toxicology. Degraded specimens usually require a cleanup step to remove the larger number of endogenous substances. This has been most commonly performed by an acid back-extraction from a solvent used in the original extraction. This acid fraction is then rebasified and extracted with more solvent. Similarly, cleanup steps can be introduced in SPE methods to enable clean extracts. Although this removes most of the endogenous substances found in putrefying tissues, it does remove neutral and many weakly ionizable substances. The benzodiazepines are a particular group of drugs lost in this process. Additional testing is therefore required to deal with a complete range of drugs and poisons.

Solid tissues such as liver, as well as muscle, fat, and even fly larvae, are similarly prepared for extraction by fine homogenization in water or a buffer. Some groups use enzyme digestion, such as with subtilisin. Most forensic laboratories use plain homogenized tissue without enzyme digestion. Unfortunately, when solid tissues are used, it is not possible to determine the actual extraction efficiency and hence the absolute content of drug in the tissue sample. Nevertheless, there is little evidence that extraction efficiencies of drug from solid tissues are likely to be much worse than with fluid specimens if suitable precautions are taken. These include a suitably fluid homogenate prepared from the solid tissue with sufficient water or buffer.

Variability in concentration of drugs has been found in muscle tissue (11,12). Variations of 20-fold are known, probably due to unequal perfusion of tissue and other postmortem artifacts; hence, it is not recommended to use this tissue alone for any quantitative purposes.

A number of other processes occur that will affect the accuracy of any drug concentration in postmortem specimens. Instability of drugs is a major factor for drugs capable of nonenzymatic bioconversion (e.g., cocaine, heroin, nitrobenzodiazepines). Consequently, assays must target alternative analytes for these drugs. A larger inherent factor is the change in concentration before sampling of a specimen even occurs. Postmortem redistribution markedly increases concentrations in blood and possibly other tissues due to leaching or diffusion from neighboring sites. This occurs most often for highly lipid-soluble drugs that have much higher muscle concentrations than the surrounding blood. To reduce the variability in postmortem drug concentrations, it has been recommended that femoral blood be used for toxicological analysis where possible. Femoral blood seems to provide a more representative concentration at the time of death. Cardiac blood is not in general a suitable sample for quantitative analysis, because concentrations of drugs are almost invariably higher in cardiac blood compared with femoral blood.

Postmortem forensic toxicology provides a bigger challenge to analytical toxicologists than those focusing exclusively on blood and urine toxicology in clinical cases. Proper validation of techniques for widely varying tissue types and conditions of tissues are required to ensure analytical reliability. Unfortunately, in many postmortem cases, artifacts caused by poor sampling, poor condition of the body, and redistribution can limit the interpretation of any analytical results.

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3-35

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Current Burden of Sudden Cardiac Death: Multiple Source Surveillance Versus Retrospective Death Certificate-Based Review in a Large U.S. Community

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OBJECTIVES We sought to determine the annual incidence of sudden cardiac death (SCD) in the general population using a prospective approach. To assess the validity of retrospective surveillance, a simultaneous comparison was made with a death certificate-based method of determining SCD incidence.

BACKGROUND Accurate surveillance and characterization of SCD in the general population is likely to significantly facilitate current and future community-based preventive and therapeutic interventions.

METHODS We performed a prospective evaluation of SCD among all residents of Multnomah County, Oregon (population 660,486) using multiple sources of surveillance. A comprehensive analysis of circumstances of death, medical records, and available autopsy data was performed. Comparisons were made with a retrospective, death certificate-based determination of SCD incidence using International Classification of Diseases-Version 10 codes and location of death.

RESULTS Between February 1, 2002, and January 31, 2003, 353 residents suffered SCD (incidence 53 of 100,000; median age 69 years, 57% male) accounting for 5.6% of overall mortality. Of these, 75 cases (21%) were identified using sources other than first responders. Resuscitation was attempted in 237 cases (67%) and successful (survival to hospital discharge) in 28 (8%). The retrospective death certificate-based review yielded 1,007 cases (incidence 153 of 100,000; median age 81 years, 51% male), and the positive predictive value of this methodology was 19%.

CONCLUSIONS Sudden cardiac death accounts for 5.6% of annual mortality, and prospective evaluation in the general population appears to be feasible. The use of multiple sources of ascertainment and information significantly enhances phenotyping of SCD cases. Retrospective death certificate-based surveillance results in significant overestimation of SCD incidence. (J Am Coll Cardiol 2004;44:1268–75) © 2004 by the American College of Cardiology Foundation

Despite recent advances in resuscitation science, survival from cardiac arrest remains low, and sudden cardiac death (SCD) is a major public health issue. However, the magnitude of SCD in the general population still remains unknown. Estimates of the annual incidence of SCD in the U.S. range from 184,000 to >400,000 (1–4). There may be two reasons for these diverse assessments. First, prospective community-based studies of SCD have not been performed. Existing studies have focused on the incidence of primary cardiac arrest as ascertained from first responder agencies (3,5,6). To reflect occurrence in the general population, multiple sources of case ascertainment should be employed, but such studies are not available. Secondly, death certificate data have been used as a surrogate for national surveillance of SCD, but the accuracy of this methodology may be limited (1,7,8). The absence of prospective evaluations of SCD involving a direct count in the general population, with evaluation at the time of the event or shortly thereafter, has been identified as a prominent "scientific gap" in our knowledge regarding SCD (1).

Prospective assessments of SCD in the general population are likely to facilitate investigative and preventive approaches to this significant public health problem. Specifically, these approaches will likely enhance the accuracy of phenotyping for this complex condition—an essential prerequisite for the application of new genomic strategies for the advancement of SCD mechanisms (9). Finally, such an approach would also furnish the prospective gold standard against which the validity of death certificate-based surveillance could be tested. We therefore performed a prospective evaluation of annual SCD incidence in a large U.S. community, using multiple sources of case ascertainment. Comparisons were made with death certificate-based determination of SCD, based on the hypothesis that this retrospective technique was likely to overestimate the incidence of SCD in the general population.

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Abbreviations and Acronyms

ACLS = advanced cardiac life support
CAD = coronary artery disease
CI = confidence interval
ICD-10 = International Classification of Diseases-Version 10
OR = odds ratio
SCD = sudden cardiac death
VF = ventricular fibrillation
VT = ventricular tachycardia

METHODS

All aspects of this investigation were approved by the Institutional Review Board, Oregon Health and Science University.

Prospective evaluation. CASE ASCERTAINMENT SOURCES. The study population included all residents of Multnomah County, Oregon (population: 660,486), irrespective of age. Residents who suffered sudden unexpected death between February 1, 2002, and January 31, 2003, were identified from several sources—the emergency medical response system, the county medical examiner's office, and 16 area hospitals. The county has a two-tiered advanced cardiac life support (ACLS) emergency medical response system. Advanced cardiac life support staffed fire engine companies provide the first response with backup by ACLS transporting ambulances. Investigators were alerted to cases either by physicians of record from the emergency medical services or by the office of the county medical examiner. Identified cases were screened to identify subjects with presumed cardiac arrest and eventually those that met the criteria for SCD (Fig. 1).

DEFINITION OF SCD. World Health Organization criteria were employed, and SCD was defined as sudden unexpected death either within 1 h of symptom onset (event witnessed), or within 24 h of having been observed alive and symptom free (unwitnessed). Subjects with non-cardiac chronic and terminal illness (e.g., terminal cancer) were excluded on the basis that such deaths were not unexpected. Additionally, all patients with an identifiable non-cardiac etiology of sudden death were excluded. Cases of sudden cardiac arrest associated with trauma, violent death, overdose, drowning, and suicide were also excluded. If they met the criteria, survivors of cardiac arrest were included under SCD cases.

POSTMORTEM EXAMINATION. Detailed information, including results of cardiac pathologic examination and toxicology screen, was obtained in all cases in which an autopsy was conducted. Autopsies were performed at the discretion of the medical examiner or attending physician. Patients with >50% stenosis in one or more coronary arteries were considered to have significant coronary artery disease (CAD). Detailed criteria for cardiac pathologic diagnosis have been published previously (10).

IDENTIFICATION OF SCD CASES. All available medical records were obtained. A comprehensive evaluation was performed for each case of unexpected death, including analysis of the circumstances of death, medical records, and available autopsy data. All collected information was assembled in a relational database. A process of in-house adjudication was employed to determine cases meeting criteria for SCD. Independent assessments were made by three cardiologists, followed by a consensus review. In the event of a disagreement regarding a specific case, the determination was based on the majority opinion.

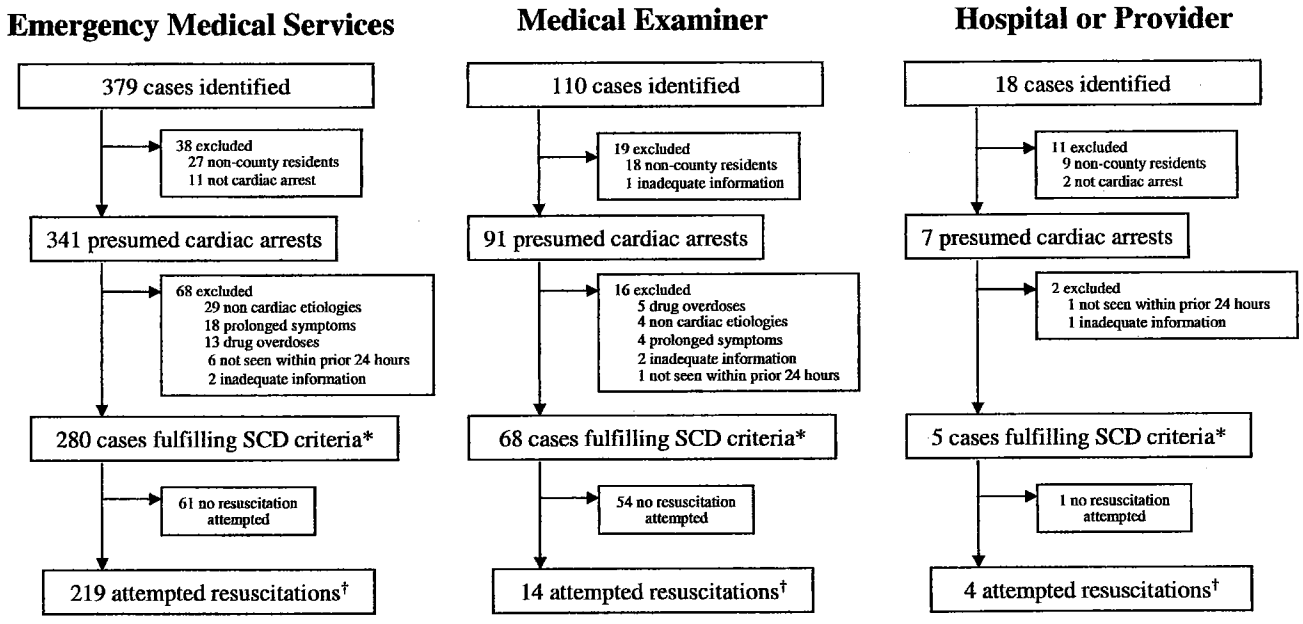

Figure 1. Details of case ascertainment and prospective identification of sudden cardiac death (SCD) cases. *353 total SCD cases in Multnomah County. †237 total attempted resuscitations.

Table 1. Subject Characteristics and Survival Outcome

	Presumed Cardiac Arrest	Prospectively Defined SCD	Death Certificate-Based SCD
Annual incidence/100,000	67*	53*	153*
Total number	439*	353*	1,007*
Female	178 (41%)	151 (43%)†	495 (49%)†
Median age (yrs)	67	69‡	81†
Witnessed	208 (47%)	184 (52%)	N/A
Attempted resuscitation	286 (65%)	237 (67%)	N/A
Return of spontaneous circulation	43 (10%)	39 (11%)	N/A
Survival to hospital discharge	29 (7%)	28 (8%)	N/A

*$p < 0.05$ for differences between the three groups (chi-square test); †$p = 0.05$ for prospective versus death certificate SCD (chi-square test for nominal variables, Wilcoxon-Mann-Whitney for medians).
N/A = not applicable; SCD = sudden cardiac death.

Retrospective evaluation using death certificates. The U.S. Centers for Disease Control and Prevention have published an estimate of the annual incidence of SCD in the U.S. based on death certificate data, and this previously described methodology was employed (2). Death certificate data were reviewed at the Oregon State Health Division on a quarterly basis. Subjects met criteria for death certificate-based SCD if they were classified under one or more specific International Classification of Diseases-Version 10 (ICD-10) codes and also died out-of-hospital or in an emergency room. The following ICD-10 codes were used: disease of heart (I00 to I09, I11, I20 to I51); congenital heart disease (Q20 to Q24); and ill-defined cause of death (R95 to R99) (2).

Statistical methods. All calculations were performed using SPSS 11.5 for Windows. Categorized nominal data were compared using the chi-square test. If any cell values were <5, the Fisher exact test was used. Categorized rates were compared using the chi-square test of equality of multinomial proportions. Medians were compared using the Wilcoxon-Mann-Whitney test. The influence of individual variables on survival to hospital discharge was estimated using odds ratios (ORs) obtained from logistic regression models. All variables were first entered individually to obtain unadjusted ORs. Variables with statistically significant coefficients were tested for predictive significance using the forward likelihood ratio method. Adjusted ORs were determined for all variables that were significantly predictive of outcome. Validity of death certificate-based SCD was assessed by determining the sensitivity, specificity, and predictive value of the technique using prospectively determined SCD as the standard. Sensitivity was the proportion of prospectively determined SCDs identified correctly, and specificity was the proportion of non-SCD cases (from overall annual mortality in the county) identified correctly. Positive predictive value was the proportion of death certificate cases that were correctly designated as SCDs.

RESULTS

Annual incidence of SCD. PROSPECTIVE EVALUATION. Between February 1, 2002, and January 31, 2003, 439 cases of presumed cardiac arrest were identified (incidence 67 of 100,000; Table 1). Of these, 353 cases met the criteria for SCD (incidence 53 of 100,000; Table 1). Details of case ascertainment as well as the process of determining cases that met the criteria for SCD are provided in Figure 1. Overall, 78% of all SCD cases were identified through the emergency medical response system, 20% through the county medical examiner's office, and 2% through local hospitals. Death certificate records for Multnomah County residents over the same time period showed that prospectively identified SCD accounted for 5.6% of all deaths among county residents (total deaths in Multnomah County, n = 6,255).

RETROSPECTIVE SURVEILLANCE. During the same time period, the retrospective death certificate-based review yielded 1,007 cases (incidence 153 of 100,000) (Table 1). Subjects identified as having SCD by retrospective death certificate review were older and more often female than subjects identified by prospective, community-based methods (Table 1). For the purpose of validating the death certificate method, survivors were not included in the comparison. Of the 325 SCD non-survivors identified by prospective methods, 193 were correctly identified by retrospective review, resulting in a sensitivity of 59%. The remainder (41%), were missed by the death certificate review for several reasons, specifically inpatient location of death (25%), diabetes as cause of death (15%), and miscellaneous other non-cardiac causes of death (60%). A total of 6,255 residents of the county died during the same time period. The death certificate method identified 5,116 non-SCDs correctly, resulting in a specificity of 86%. Of the cases designated as SCD by the death certificate method, only 193 were identified correctly, resulting in a positive predictive value of 19%.

Detailed description of prospectively defined SCD cases. AGE AND GENDER. In residents age <35 years, the highest incidence was observed in the 0- to 5-year age group (Fig. 2). Over 35 years of age, the highest incidence was observed in the 75- to 84-year age group. Approximately 25% of all SCD cases occurred at age <65 years. The gender- and age-based composition of prospectively deter-

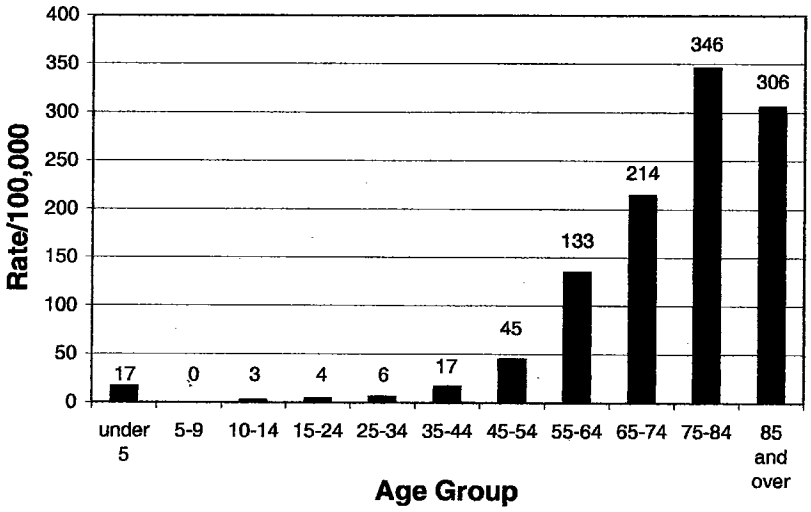

Figure 2. Age-based annual incidence of sudden cardiac death among residents of Multnomah County, Oregon (population 660,486).

mined SCD cases is shown in Figure 3. Overall, 43% of SCD cases were female.

ETIOLOGY OF SCD. Previous medical records were obtained in 53% of cases, and a further 4% were confirmed as not having seen a physician before death. Overall, 50% of cases over age 35 years had CAD that had been identified (Table 2). Nine patients had aortic stenosis with varying degrees of severity (severe, n = 1; moderate, n = 3; mild to moderate, n = 3; mild n = 2). Four patients had congenital heart disease. The two cases in the <35 years age group (non-autopsy) were Ebstein's anomaly with Wolff-Parkinson-White syndrome and congenital aortic valve disease with two prosthetic valve replacements. Autopsies were conducted in 12% of all cases (n = 41) (Table 3). Associated CAD was observed exclusively in subjects age 35 years or older and was observed in 76% of this age group. Significant stenosis of the coronary arteries was observed in the majority of cases, but plaque rupture with thrombus was uncommon and was identified in only one subject with CAD. In the >35 years age group, one patient had severe pulmonic stenosis (previously repaired ventricular septal defect) and a second had a bicuspid aortic valve.

LOCATION OF SCD. Eighty-two percent of arrests took place at home, of which 46% were witnessed. The location did not vary significantly when stratified by age or gender (range, 79% to 86% at home). Thirty-four arrests (9.6%, 21 witnessed) took place in care facilities (nursing care, rehabilitation, adult foster care, assisted living, and the like) or doctors' offices. Eight arrests (2.2%), all witnessed, took place in non-residential "community units" (schools, sports centers, malls, churches) (11). Overall, 52% of SCDs were witnessed.

SURVIVAL OUTCOME. Among SCD, resuscitation was attempted in 237 cases (Table 1). A multiple regression analysis showed that only the ratio of ventricular fibrillation (VF) to ventricular tachycardia (VT) and arrest location

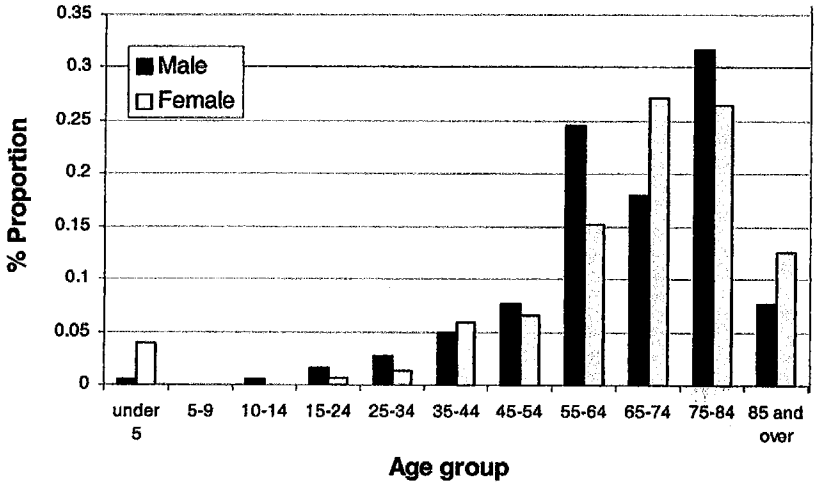

Figure 3. Gender- and age-based composition of prospectively determined sudden cardiac death cohort.

Table 2. Conditions Associated With Sudden Cardiac Death*

Associated Conditions	Age <35 Yrs	Age ≥35 Yrs	All Ages
Number of cases	19	169	188
Coronary artery disease	0†	84 (50%)†	84 (45%)
CHF/cardiomyopathy	0†	46 (27%)†	46 (25%)
Aortic stenosis	0	9 (5.3%)	9 (4.8%)
Congenital heart disease	2 (10%)	2 (1.1%)	4 (2.1%)
Seizure disorder	1 (5.2%)	12 (7.1%)	13 (6.9%)
No significant associated conditions	14 (74%)	55 (32%)	69 (37%)

*Analysis is limited to subjects with availability of previous clinical records/autopsy results (n = 188). †Age groups <35 yrs versus ≥35 yrs, $p < 0.05$ (Fisher exact test).
CHF = congestive heart failure.

were significant predictors of survival. If the presenting arrhythmia was VF/VT, the adjusted OR for survival was 10.2 (95% confidence interval [CI] 2.9 to 36). If the arrest took place outside the home, the adjusted OR was 3.1 (95% CI 1.3 to 76). The frequency of each variable among survivors and non-survivors is listed in Table 4. The overall survival rate when patients presented with VF or pulseless VT was 24%, compared with 2% when patients presented with pulseless electrical activity or asystole ($p < 0.001$, Fisher exact test) (Fig. 4). For SCD cases who presented with VF/VT and had a witnessed cardiac arrest, survival to hospital discharge was 29%. Females had a lower rate of VF compared with males (35.3 vs. 50%, $p = 0.019$, Fisher exact test). Survival in VF cases was not significantly different between genders (females 25.7% vs. males 23.7%, $p = 0.51$, chi-square test), but survival in pulseless electrical activity/asystole cases occurred only among women (4.7%). Overall survival to hospital discharge among the subgroup of SCD subjects who underwent resuscitation was identical in men and women (11.8%).

CHRONOBIOLOGICAL ASSOCIATIONS. A strong diurnal trend for the occurrence of SCD was observed. The 4-h period with the greatest event rate was between 8 AM and noon, with 27% of cases, whereas the lowest event rate was between midnight and 4 AM, with 8% of cases ($p < 0.001$, chi-square test). Significant daily or seasonal variations in occurrence of SCD were not observed.

DISCUSSION

Summary of main findings. In this prospective evaluation of a large U.S. community, the annual incidence of SCD was 53 per 100,000 residents and accounted for 5.6% of overall deaths. Eighty-two percent of SCDs took place at home, and 43% of cases were female. Among patients over age 35 years who underwent autopsy, significant CAD was observed in 76%. Overall survival to hospital discharge was 8%. In a multivariate model, survival was dependent on VT/VF being the presenting arrhythmia (OR 10.2, CI 2.9 to 36.0) and location of SCD occurrence outside the home (OR 3.1, CI 1.3 to 7.6). The retrospective, death certificate-based method of surveillance resulted in an almost threefold overestimation of annual SCD incidence.

Although there is a lack of studies of SCD that use multiple sources, there are several studies that have prospectively examined the community incidence of primary cardiac arrest using data collected by first responders. The incidence of primary cardiac arrest and SCD in the present study is lower than some published studies, but it is also higher than others. From several studies, the annual incidence of treated primary cardiac arrest has ranged between 41 and 89 of 100,000 (3,12–15). If we use presumed cardiac arrest cases to calculate the annual incidence in the present study (n = 439), this figure is 67 of 100,000 residents (Table 1). A prospective study in the Maastricht area of the Netherlands reported an annual incidence of sudden out-of-hospital cardiac arrests of 90 to 100 of 100,000 residents age 20 to 75 years (16). On the other hand, a retrospective study of SCD among residents of southern Okinawa, Japan that employed multiple sources reported a

Table 3. Cardiac Abnormalities Identified in the Autopsy Subgroup (n = 41)

	Age <35 Yrs	Age ≥35 Yrs	All Ages
Number of subjects	12	29	41
Coronary artery disease	0*	22 (76%)*	22 (54%)
Cardiac rupture	0	1 (4%)	1 (3%)
Myocarditis	0	1 (3%)	1 (2%)
Congenital heart disease	0	2 (7%)	2 (4%)
Aortic dissection	0	1 (3%)	1 (2%)

*Age groups <35 yrs versus ≥35 yrs, $p < 0.05$ (Fisher exact test).

Table 4. Comparison Between Cardiac Arrest Survivors and Non-Survivors Among SCD Cases That Underwent Resuscitation (n = 237)

	Survivors	Non-Survivors
Total	28	209
Mean age (yrs)	65	67
Median age (yrs)	68	70
Males	16 (57%)	118 (56%)
Witnessed arrest	28 (100%)*	141 (68%)*
Location of arrest		
Home	13 (46%)*	170 (81%)*
Work	2 (7%)	4 (2%)
Emergency department	3 (11%)*	2 (1%)*
Terminal arrhythmia reported	27 (96%)	198 (95%)
VF/VT	24 (86%)*	74 (34%)*
PEA/asystole	3 (11%)*	124 (63%)*

*$p < 0.05$ for survivors versus non-survivors (chi-square test for location-home, Fisher exact test for all others).
PEA = pulseless electrical activity; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.

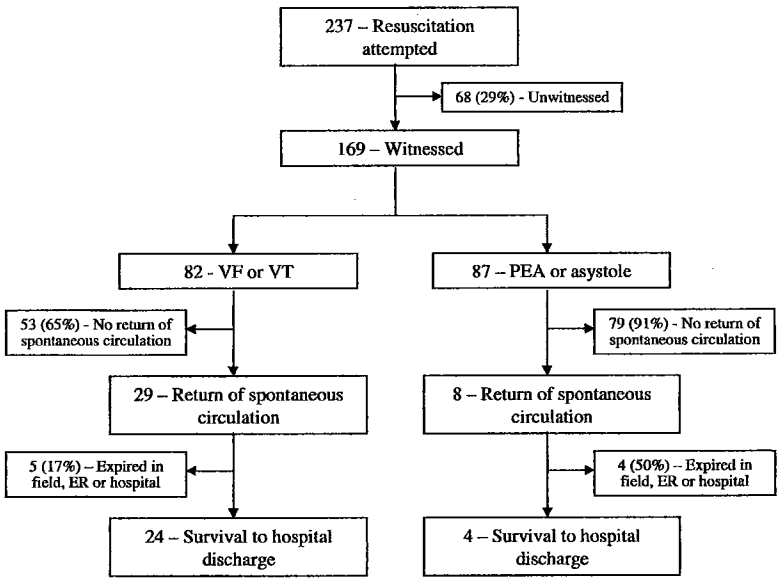

Figure 4. Outcome of attempted resuscitations. A modified Utstein-style template has been used for witnessed arrests. ER = emergency room; PEA = pulseless electrical activity; VF = ventricular fibrillation; VT = ventricular tachycardia.

crude annual incidence rate of 37 per 100,000 residents—lower than the rate observed in the present study (17).

Because the present study examined the incidence of SCD (not primary cardiac arrest) among all age groups, the overall objective as well as the definition employed were different from previous studies. Also, multiple sources of case ascertainment were employed. In addition to first responders, the medical examiner and area hospitals and physicians reported cases. In addition to data from first responders, access to hospital records, circumstances of death, and autopsy information likely enabled a broader and more efficient exclusion of non-cardiac etiologies of sudden death. For instance, on the grounds that such deaths are not unexpected, patients who died after a non-cardiac terminal illness such as cancer were excluded. As a result, although the incidence is lower, the results are likely to be a more accurate assessment of the occurrence of sudden death directly related to a cardiac etiology in the general population. As shown in Figure 1, 99 of 379 cases (26%) initially ascertained via the emergency medical services eventually did not meet the criteria for SCD. If the present study had limited case ascertainment to first responders, only 280 (80%) of total SCD cases would have been identified, resulting in a significant underestimation. However, it is possible that we were unable to track some cases of SCD, which may have contributed to a likely modest underestimation of incidence. The first category may be patients with unwitnessed SCD who were discovered more than 24 h after their death. Also, county residents who suffered SCD while traveling out of state may also not have been ascertained. The major source of case ascertainment were the first responders (single company with 33 ambulances and 150 paramedics), and we tracked every sudden cardiac arrest on a daily basis. The second major source was the county medical examiner. In the state of Oregon, all deaths that do not occur in a hospital have to, by law, be reported to the medical examiner. We reviewed every death reported to the medical examiner on a daily basis to identify cases of SCD among these. Because all cases of SCD have to be unexpected, as reported universally in previous studies, hospitals are an unlikely source of SCDs—hence the small number from area hospitals. Hence it is very likely that we captured the vast majority of SCDs that occurred in Multnomah County.

The gender distribution of SCD in the general population was significantly different from that previously reported among treated cases of primary cardiac arrest. In the present study, the gender difference in SCD occurrence was low (57% male vs. 43% female), whereas most studies of primary cardiac arrest have reported a threefold higher incidence in men compared with women (18). This probably reflects the differences in the way cases were ascertained and defined in the two types of populations. In the present study, among patients with primary cardiac arrest who underwent resuscitation, women had a lower prevalence of VF and a higher rate of pulseless electrical activity as the presenting arrhythmia. This trend is similar to previously reported findings (18). There were no differences between genders with respect to the overall survival rate.

As reported by others, there was a strong association between the nature of the presenting arrhythmia and survival among the subjects who underwent resuscitation. Our rates of survival from VF and pulseless electrical activity/asystole (24% and 2%, respectively) show trends similar to the Seattle experience reported recently by Cobb et al. (32% and 3.5%) (3). In the present study, when the onset of SCD was witnessed and the presenting arrhythmia was VF/VT,

JACC Vol. 44, No. 6, 2004
September 15, 2004:1268–75

survival to hospital discharge was 29%. The overwhelming majority (82%) of SCDs occurred at home. These findings are identical to the observations made in the Maastricht study that evaluated primary cardiac arrest (16). The survival rate was better if the SCD occurred outside the home. This is likely related to a higher chance of the out-of-home SCD being a witnessed event (70% out-of-home SCDs were witnessed, compared with 46% of in-home SCDs, $p < 0.05$, chi-square test). As observed in the present study for SCD, previous investigations have found similar evidence of a circadian rhythm for occurrence of primary cardiac arrest (19,20). Among 1,019 primary cardiac arrests, Levine et al. observed that the frequency of cardiac arrests increased significantly from 6 AM until noon (20).

Because of the prospective nature of this investigation, community medical records could be obtained in a significant number of subjects (53%). Earlier autopsy series and studies of survivors have reported that approximately 50% of cases may present with SCD as the first and only manifestation of heart disease. Thus, it is likely that this subgroup constituted a significant number of cases for which medical records were not obtained. As expected, CAD dominated the conditions associated with SCD, and similar to previous observations, 76% of autopsied cases in the over 35 years age group had significant CAD (21,22). Heart failure, aortic stenosis, and congenital heart disease have also been previously associated with an increased risk of SCD. Among non-cardiac conditions, the association with seizure disorder is a recurring finding (10,23,24), but mechanisms and the pathophysiologic links between the two conditions remain unclear.

In the present study, death certificate-based retrospective surveillance resulted in a significant overestimation of SCD incidence. The annual incidence of 153 of 100,000 residents using this retrospective method is very similar to the rate observed nationally for the U.S. (162 of 100,000) using the same methodology (2). Although previous studies have pointed out the potential limitations of using death certificate data to determine SCD cases, comparisons with prospectively conducted incidence evaluation of SCD have not been available. Iribarren et al. (7) examined the validity of death certificate diagnosis of out-of-hospital SCD in a retrospective six-year mortality study. Compared with retrospectively obtained physician diagnosis of SCD, sensitivity was 87% and specificity 66%. Only 27% of the cases labeled SCD by death certificate agreed with the physician diagnosis. Every et al. (8) performed a retrospective comparison of death certificate-based SCD in high-risk patients with a paramedic-based classification system for cardiac arrest. They reported a sensitivity ranging from 78% to 85% and specificity 25% to 58% (8). In the present study, sensitivity and specificity were 59% and 86%, respectively. However, given the significant overestimation, the positive predictive value of death certificate-based determination of SCD was only 19%, that is, only 19% of death certificate-designated SCDs agreed with the prospectively defined SCDs. Given the findings of the present study, death certificate-based surveillance, as presently employed, is unlikely to be a useful surveillance tool for SCD. For SCD, definitions and criteria should be employed prospectively among cases that occur in the general population, and based on our findings, such an evaluation should be feasible. Using this technique in a sample of representative U.S. communities could provide a more accurate assessment of the national incidence and the prevalence of SCD.

Conclusions. The SCD burden contributed to 5.6% of annual mortality in this large U.S. community, with an unexpectedly narrow difference between genders. Likelihood of successful resuscitation continues to be low but is strongly associated with VF/VT being the presenting arrhythmia. Retrospective, death certificate-based surveillance results in a significant overestimation. Prospective evaluation of SCD incidence using multiple sources appears to be feasible.

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[Articles] ◄ Previous Article | Table of Contents | Next Article ►

Digoxin Level and Clinical Manifestations as Determinants in the Diagnosis of Digoxin Toxicity

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Summary:

The aim of this study was to determine the relative importance of different risk factors in the diagnosis of digitalis toxicity. The authors recruited inpatients for whom serum digoxin level was requested and prospectively followed them for a week to ascertain if they showed digitalis toxicity. The predictive value of different factors for the assessment of digoxin toxicity was analyzed by multiple logistic regression. Forty-one toxic and 58 nontoxic patients were included. In the univariant analysis, intoxicated patients were older, most were women, and they had worse renal function and higher digoxin level; but there were no differences in serum electrolytes or other risk factors. In the multivariant analysis, digoxin level was the only independent factor related to digitalis toxicity. A different risk of toxicity for each clinical manifestation was found for a certain digoxin level. Patients with signs of automaticity in the electrocardiogram had a higher likelihood of being intoxicated than patients with gastrointestinal symptoms, atrioventricular block, or bradycardia. Therefore, in the population evaluated in this study, digoxin level is the key independent factor in digoxin intoxication, although the probability of being intoxicated is also a function of the type of clinical manifestations. A graphic approximation of this probability based on these two factors is presented.

Digoxin is a commonly prescribed drug, and the problem of digoxin toxicity is well recognized. Several studies performed in the 1970s showed that toxic effects developed in 6% to 29% of all patients taking digitalis (1-4). Although the incidence is smaller (2-5%) in more recent studies (5-8), digoxin is still a common cause of visits to emergency units and hospital admissions (3,9). In the emergency ward of our hospital, digitalis toxicity constitutes 3% of mild adverse drug reactions, 5% of moderate ones, and 4% of severe ones (10), and it is the second most common cause of drug-related hospital admissions (11). Moreover, digitalis intoxication increases the length of hospitalization, and mortality was reported in 3-21% of patients who had clinical toxicity (4).

Several factors have been reported to modify the sensitivity of the myocardium to digoxin and to increase or decrease digitalis toxicity. Thus, hypokalemia, hypomagnesemia, hypercalcemia, hypoxia, ischemic heart disease, hypothyroidism, drug interactions, and advanced age all increase the likelihood of digitalis toxicity, while hyperthyroidism,

childhood, and atrial fibrillation decrease it (4,12,13). All these factors interact (1,2,14-16), and it is probably the interrelation of all the factors present in a subject that determines the presence and extent of toxicity (17). However we do not know the relative contribution of each factor to the presence of toxicity.

The clinical diagnosis of digoxin intoxication is frequently difficult because the symptoms and electrocardiographic changes are nonspecific. There is controversy about the usefulness of serum digoxin levels in the diagnosis of digitalis intoxication because, as it is known, some overlap exists between "therapeutic" and "toxic" concentrations in relation to clinical symptoms of intoxication and vice versa. Despite this, serum digoxin level is an important predictor of digoxin toxicity and the most important predictor of mortality (6), and it is positively associated with mortality rate in patients treated with digoxin (18).

The aim of this prospective study was to determine the relative importance of every one of those factors reported as risk factors for digitalis toxicity (sex; age; digoxin level; concomitant drugs and diseases; serum sodium, potassium, magnesium, and calcium; and renal function), and to ascertain the role of serum digoxin level in the diagnosis of digitalis toxicity.

Back to Top

METHODS

We recruited inpatients taking digoxin from the requests for routine therapeutic digoxin monitoring received in the Clinical Pharmacology Service of "Hospital La Paz" during a period of 1-½ years. Patients were included in the study if they were age 14 years or older and if the venous blood sample had been obtained more than 6 hours after their last digoxin dose. They could be admitted in any service of this general hospital. We excluded patients with overdose intoxication and those having a pacemaker. We included all patients whose doctors suspected intoxication, and one or two patients randomly selected every day from the other serum digoxin requests. Patients were always selected for inclusion in the study before the digoxin concentration test was performed.

For a definitive classification of patients suffering from digoxin toxicity we established the criteria following those of other authors (15,19) (Table 1). Patients meeting any criteria of toxicity were classified as toxic provided this criteria disappeared after a week of digoxin withdrawal or dose reduction. Subjects meeting no criteria, and those meeting any criteria that either disappeared without digoxin withdrawal or that did not disappear after digoxin withdrawal were classified as nontoxic. Patients meeting any criteria in whom digoxin was not withdrawn and the criteria persisted were excluded.


Table 1

Digoxin level and serum ions (potassium, sodium, magnesium, and calcium) were estimated in the same serum sample. Serum digoxin was measured by fluoroimmunoassay using the Abbott TDX system. If the sample was hemolyzed the patient was excluded for potassium, magnesium, and sodium, because hemolysis can alter serum ions. Also, the creatinine clearance for each patient was calculated through the Cockroft and Gault equation (20). Between 2 and 4 hours after the sample extraction, a full clinical assessment of each subject was performed by one of the investigators in a case-record form and an electrocardiogram was obtained. The physicians attending the patients were told about the digoxin level but not about this study. Patients were prospectively followed for at least 1 week by the same investigator.

Patients classified as toxic and nontoxic were compared univariantly using unpaired *t*-test and chi-square test. Results are reported as mean ± standard error of mean (M ± SEM) for numerical data and percentages for qualitative variables. A stepwise multiple logistic regression (BMDP Statistical Software) was carried out including all independent variables (sex; age; concomitant drugs or diseases; creatinine clearance; serum sodium, potassium, magnesium, and calcium; and digoxin level) to evaluate their predictive value for the assessment of digoxin toxicity. Although signs and symptoms are nonindependent factors, another analysis including them (grouped as automaticity, bradycardia or block, and gastrointestinal symptoms) was performed to evaluate the relative weight of each one to the digoxin toxicity status and their relationship

3-48

with digoxin level. Odds ratio and 95% confidence intervals were calculated for the significant independent variables from the coefficients and standard errors of the logistic regression.

Back to Top

RESULTS

A total of 109 patients were included; 10 of them were excluded because they were discharged from the hospital in less than a week (5 patients) or because they continued taking digoxin in spite of meeting some of the criteria (5 patients). Nine patients were not considered for potassium, magnesium, and sodium because they had hemolyzed serum samples (5 patients), their serum samples were lost (3 patients) and we could not measure the ions, or they showed a severe acidosis that modified serum ions (1 patient).

Forty-one of the 99 evaluable patients (10 male, 31 female; mean age 76.6 years) were classified as toxic and 58 (28 male, 30 female; mean age 71.7 years) as nontoxic. Table 1 shows the electrocardiographic disturbances and symptoms presented by these patients according to the diagnosis of toxicity.

At least one symptom of toxicity was present in 53 patients, and 41 (77.4%) of them were finally toxic. Gastrointestinal symptoms were present in 29 patients, and 24 (82.8%) of those were ultimately toxic. In 25 patients there were electrocardiographic signs of automaticity (premature ventricular beats or tachycardia); 23 (92.0%) of them were finally toxic. Bradycardia or atrioventricular block were present in 24 patients, 15 (62.5%) of whom were classified as toxic.

The characteristics of the patients with digoxin intoxication were univariantly compared with those of the nontoxic subjects (Tables 2 and 3). Intoxicated patients were more frequently women, were older, had a smaller body mass, and had worse renal function. As expected, serum digoxin levels were significantly higher in toxic patients (3.08 ± 0.20 ng/mL) than in nontoxic ones (1.58 ± 0.10 ng/mL), but there was considerable overlap between the two groups. Digoxin level was below 2 ng/mL in 10 intoxicated patients and higher than 2 ng/mL in 16 asymptomatic subjects.

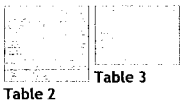
Table 3
Table 2

There were no significant differences between the two groups in serum electrolytes (Table 3), the frequency of ischemic heart disease, heart failure, atrial fibrillation, treatment with diuretic or antiarrhythmic drugs (Table 2), or incidence of electrolyte abnormalities. Only 4 toxic and 5 nontoxic patients had hypokalemia (<3.5 mEq/L), 4 toxic and 4 nontoxic patients had hypomagnesemia (<1.6 mEq/L), and 6 toxic and 3 nontoxic patients had hypercalcemia (>10.6 mg/dL).

The doctor who requested the digoxin level determination suspected digoxin toxicity in 78.1% of toxic patients and in 24.1% of nontoxic patients (Table 2). Thus 23 patients (23%) were incorrectly diagnosed. It is probable that this percentage would be smaller in a study specifically designed to examine this aspect.

Toxicity developed in 10 patients with serum digoxin levels lower than 2 ng/mL. Three of them had hypokalemia and another 3 had hypomagnesemia. These 10 patients had lower serum potassium concentrations than the other toxic patients with digoxin levels higher than 2 ng/mL (3.84 ± 0.12 vs. 4.79 ± 0.19 mEq/L, p = 0.006). Serum magnesium levels were also somewhat lower in toxic subjects with low digoxin concentrations, though this difference did not reach statistical significance (1.95 ± 0.15 vs. 2.13 ± 0.07 mEq/L, p = 0.205).

Logistic regression analysis including independent variables showed that only serum digoxin level was significantly associated with digoxin intoxication. None of the other independent variables improved the statistical prediction. As in the univariant analysis, serum potassium, magnesium, and calcium; ischemic heart disease; and other variables that have been considered in the literature as risks factors for digoxin toxicity did not improve the statistical prediction. Age, sex, weight, dose, and creatinine clearance, which showed statistical differences between toxic and nontoxic patients in univariant analysis, lost their

significant association in multivariant analysis, probably because they correlate with digoxin level.

Multivariant analysis including toxicity criteria (grouped as shown in Table 2) confirmed the statistical significance of the association between serum digoxin concentration and diagnosis of toxicity. They also showed that signs of automaticity are more strongly associated to toxicity, while gastrointestinal symptoms and bradycardia or atrioventricular block present a weaker association (Table 4).


Table 4

Based on the logistic regression, it is possible to draw a figure showing the probability of intoxication at a digoxin concentration for patients having a specific manifestation of toxicity (Fig. 1). We can see that, for the same serum digoxin level (e.g., 2 ng/mL), a patient with electrocardiographic signs of automaticity has a higher likelihood of being intoxicated (about 80%) than a patient with gastrointestinal symptoms or bradycardia (lower than 40%). The association of bradycardia and gastrointestinal symptoms increase the risk to the level found with isolated automaticity signs, and the association of this with any other sign or symptom increases the risk of toxicity to more than 90% at a 2 ng/mL level.


Fig. 1

Back to Top

DISCUSSION

Inpatients included in this study were selected from those whose attending physician asked for a serum digoxin determination. Therefore they are not a representative sample of all patients treated with digoxin. However we think that the sample included represents those patients that are more difficult to manage and in whom digoxin determination would be more useful. In any case this point should be taken into account in the interpretation of these results.

Most of the variables included in this study are generally considered as risk factors for digoxin toxicity. Our study shows digoxin level as the only important risk factor. In fact, in most of the published studies (1-3,6,8,14-16,19,21), serum digoxin is the only factor that is significantly higher in toxic than in nontoxic patients; the exceptions are two studies that included patients with digoxin levels higher than 3 ng/mL (22,23) and another study of seriously ill patients with more than one digoxin determination (24). In another study in which all the intoxicated patients had very low digoxin levels (19), serum digoxin was not an independent predictor of digitalis intoxication. Nevertheless, we have tried a logistic regression analysis with patients having digoxin levels lower than 2 ng/mL and serum digoxin level remained the only independent predictor of intoxication.

Digoxin concentrations show some overlap between toxic and nontoxic patients. This overlap has been classically attributed in part to various extra-cardiac factors which could influence the distribution of digoxin in the body (e.g., sex, age, and renal failure) or the response of the heart to the drug (e.g., electrolyte abnormalities) (15). The results in our study show that these factors are probably less important than usually considered. Inasmuch, a detailed review of the literature data shows that each factor has been found related to toxicity in very few studies (and frequently in only one), as set out below.

Hypokalemia has long been recognized as an important risk factor for the development of digitalis intoxication (15,25,26). However, old and recent studies did not show differences in potassium levels between toxic or nontoxic patients (1-3,7,8,14,15,19,21), nor between patients receiving or not receiving diuretics (19,21). In the present and in many other clinical studies serum potassium was not found to be a predictor of digoxin toxicity (6,7,19,23). Currently the incidence of hypokalemia is smaller than in older studies (15) because the risk of potassium depletion is widely appreciated and patients are frequently given potassium supplements or potassium-sparing drugs. Conversely, digoxin intoxication can produce hyperkalemia, and in some studies potassium is higher in toxic than in nontoxic patients (3). In fact, in our study there is a significant positive correlation between serum potassium and digoxin level ($r = 0.36$, $p = 0.006$), and this could explain why toxic patients with digoxin levels below 2 ng/mL have lower potassium levels than toxic patients with higher digoxin levels.

3-50

Magnesium is less likely to be monitored or administered, and hypomagnesemia should be more common than hypokalemia. Hypomagnesemia has been associated with digoxin toxicity in one study (19), but this is not the case in our study. Neither did any other authors find any relation between magnesium concentrations and digoxin toxicity (8,16,21).

As in our study, several authors have associated impaired renal function with digoxin toxicity (1,2,6,7,14), but the creatinine clearance is not a predictor of digoxin intoxication because its effect could be fully explained by the increased digoxin level (6). Nevertheless, Piergies et al (23) found that impaired renal function increases the risk of toxicity for patients with high digoxin levels.

Several authors have shown a correlation between advanced age and adverse drug reactions to digoxin (2,4,7,14), which can be a result of the physiologic changes seen in the elderly, such as decrease muscle mass and decrease renal function (1,14). This correlation could not be confirmed in the present and other studies (5).

Some authors have found that a higher proportion of toxic patients are women (5,8,23,27), but the numbers are statistically insignificant. In our study, intoxication was most frequent in women, probably because they were older than men (77.0 ± 1.1 vs. 68.4 ± 2.2 years, p = 0.0002), with lower muscle mass (weight and height significantly smaller), and with higher serum digoxin levels: 2.4 ± 0.16 ng/mL vs. 1.88 ± 1.73 ng/mL, p = 0.0412).

Therefore, in agreement with most of the published evidence, our study shows that digoxin level is the key independent factor in digoxin intoxication. All other factors appear to play a minor role in the whole population, although they may be important in a small group of patients. So serum digoxin determination should be one of the most important diagnostic tests in a patient with suspected digoxin toxicity.

A previous observation of Sonnenblick et al (16) shows that patients with gastrointestinal symptoms of digoxin toxicity had higher serum digoxin levels than those with digoxin-induced automaticity, suggesting different thresholds for the different manifestations of digoxin toxicity. Our study confirms that different clinical manifestations carry different risks of intoxication.

The usefulness of serum digoxin determination has been debated in the literature because of the lack of a clear therapeutic window and the overlap between "therapeutic" and "toxic" concentrations, as in fact happens with every drug. Diagnosis of toxicity is one of the most frequent reasons for digoxin monitoring, but the mentioned overlap makes difficult to do a diagnosis in many cases. In fact, to look for a certainty about diagnosis of digitalis toxicity is unrealistic at the present state of knowledge, and it would be more helpful to analyze which probabilities can improve our performance in this decision-making process. In our opinion the results obtained in this study give an estimation of these probabilities and could aid in this process on the basis of clinical signs and digoxin level.

Back to Top

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This work was done in Hospital Universitario La Paz.

Back to Top

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3-51

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Key Words: Digoxin toxicity; Digoxin level; Inpatients; Therapeutic drug monitoring

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IMAGE GALLERY

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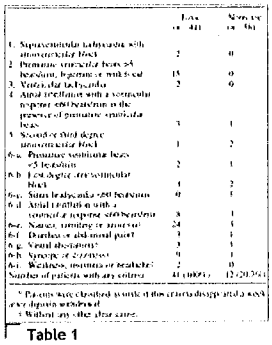

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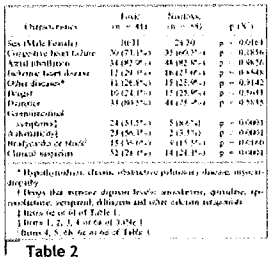

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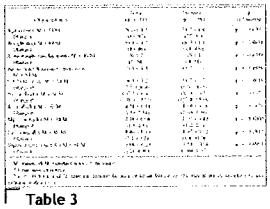

Table 3

TABLE 1.

	Toxic (n 41)	Nontoxic (n 58)
1. Supraventricular tachycardia with atrioventricular block	2	0
2. Premature ventricular beats >5 beats/min, bigemini or multifocal	15	0
3. Ventricular tachycardia	2	0
4. Atrial fibrillation with a ventricular response <60 beats/min in the presence of premature ventricular beats	3	1
5. Second or third degree atrioventricular block	1	2
6-a. Premature ventricular beats <5 beats/min	2	1
6-b. First degree atrioventricular block	3	2
6-c. Sinus bradycardia <60 beats/min	0	1
6-d. Atrial fibrillation with a ventricular response <60 beats/min	8	3
6-e. Nausea, vomiting or anorexia†	24	5
6-f. Diarrhea or abdominal pain†	3	1
6-g. Visual aberrations†	3	1
6-h. Syncope or dizziness†	9	1
6-i. Weakness, insomnia or headache†	2	0
Number of patients with any criteria	41 (100%)	12 (20.7%)

* Patients were classified as toxic if this criteria disappeared a week after digoxin withdrawal.
† Without any other clear cause.

Digoxin Level and Clinical Manifestations as Determinants in the Diagnosis of Digoxin Toxicity.
Abad-Santos, Francisco; Carcas, Antonio; Ibanez, Carmen; Frias, Jesus

Therapeutic Drug Monitoring. 22(2):163-168, April 2000.

TABLE 1. Criteria for the diagnosis of digoxin toxicity and number of patients meeting any criteria the first study day**Patients were classified as toxic if this criteria disappeared a week after digoxin withdrawal.+Without any other clear cause.

TABLE 2.

Characteristics	Toxic (n = 41)	Nontoxic (n = 58)	p (X^2)
Sex (Male/Female)	10/31	28/30	p = 0.0161
Congestive heart failure	30 (73.1%)	35 (60.3%)	p = 0.1856
Atrial fibrillation	34 (82.9%)	48 (82.8%)	p = 0.9826
Ischemic heart disease	12 (29.3%)	16 (27.6%)	p = 0.8548
Other diseases*	11 (26.8%)	15 (25.9%)	p = 0.9142
Drugs†	10 (24.4%)	15 (25.9%)	p = 0.8681
Diuretics	33 (80.5%)	44 (75.9%)	p = 0.5855
Gastrointestinal symptoms‡	24 (58.5%)	5 (8.6%)	p = 0.0001
Automaticity§	23 (56.1%)	2 (3.5%)	p = 0.0001
Bradycardia or block‖	15 (36.6%)	9 (15.5%)	p = 0.0160
Clinical suspicion	32 (78.1%)	14 (24.1%)	p = 0.0001

* Hypothyroidism, chronic obstructive pulmonary disease, myocardiopathy.

† Drugs that increase digoxin levels: amiodarone, quinidine, spironolactone, verapamil, diltiazem and other calcium antagonists.

‡ Items 6e or 6f of Table 1.

§ Items 1, 2, 3, 4 or 6a of Table 1.

‖ Items 4, 5, 6b, 6c or 6d of Table 1.

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TABLE 2. Qualitative variables in patients with or without digoxin toxicity*Hypothyroidism, chronic obstructive pulmonary disease, myocardiopathy.+Drugs that increase digoxin levels: amiodarone, quinidine, spironolactone, verapamil, diltiazem and other calcium antagonists.++Items 6e or 6f of Table 1.[S]Items 1, 2, 3, 4 or 6a of Table 1.[//]Items 4, 5, 6b, 6c or 6d of Table 1.

3-55

TABLE 3.

Characteristics	Toxic (n = 41)	Nontoxic (n = 58)	p (t Student)
Age (years) M ± SEM	76.6 ± 1.5	71.7 ± 1.6	p = 0.0369
(Range)	(49–92)	(22–86)	
Weight (kg) M ± SEM	59.8 ± 1.7	66.3 ± 1.5	p = 0.0054
(Range)	(40–80)	(40–100)	
Dose/weight (μg/kg/week) M ± SEM	26 ± 2	25 ± 1	p = 0.6358
(Range)	(7–54)	(9–54)	
Initial heart frequency (beats/min) M ± SEM	75.3 ± 3.5	87.7 ± 3.1	p = 0.0098
CrCl (mL/min) M ± SEM	36.3 ± 3.2	51.7 ± 3.7	p = 0.0038
(Range)*	(7.2–126.4)	(6.3–136.5)	
Na^+ (mEq/L) M ± SEM	137.3 ± 0.9	139.0 ± 0.7	p = 0.1177
(Range)†	(128.9–157.6)	(127.0–150.6)	
K^+ (mEq/L) M ± SEM	4.54 ± 0.16	4.29 ± 0.10	p = 0.1678
(Range)†	(3.39–7.34)	(2.59–5.95)	
Mg^{++} (mEq/L) M ± SEM	2.08 ± 0.06	2.07 ± 0.04	p = 0.8260
(Range)†	(1.5–2.9)	(1.2–2.7)	
Ca^{++} (mg/dL) M ± SEM	8.86 ± 0.16	8.97 ± 0.12	p = 0.5917
(Range)	(7.2–11.2)	(6.8–11.0)	
Digoxin level (ng/mL) M ± SEM	3.08 ± 0.20	1.58 ± 0.10	p = 0.0001
(Range)	(1.21–6.90)	(0.44–3.37)	

M, mean; SEM, standard error of the mean.
* Creatinine clearance.
† n = 39 toxic and 51 nontoxic patients because of serum hemolysis (5), loss of serum samples (3), and extreme acidosis (1).

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TABLE 3. Quantitative variables in patients with or without digoxin toxicityM, mean; SEM, standard error of the mean.*Creatinine clearance.+n = 39 toxic and 51 nontoxic patients because of serum hemolysis (5), loss of serum samples (3), and extreme acidosis (1).

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TABLE 4.

Variable	β	p	Odds ratio	95% confidence interval
Digoxin level	1.505	<0.01	4.51†	1.62–12.5
Gastrointestinal symptoms	2.117	0.011	8.31	1.59–43.5
Bradycardia or block	1.532	0.089	4.63	0.784–27.3
Automaticity	3.810	<0.001	45.2	7.14–285.0
Constant	−5.552	<0.001		

* By logistic regression analysis.
† For every 1 ng/mL increase.

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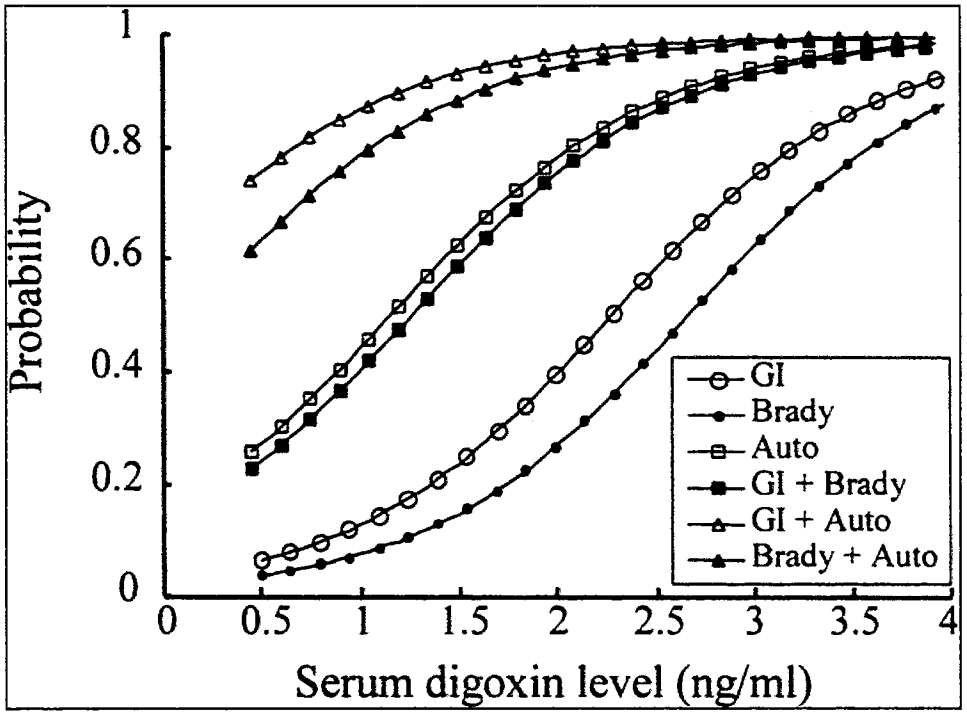
TABLE 4. Relative values of the best predictors for digoxin toxicity and their odds ratios**By logistic regression analysis.+For every 1 ng/mL increase.

FIG. 1.



Digoxin Level and Clinical Manifestations as Determinants in the Diagnosis of Digoxin Toxicity.
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FIG. 1. Probability of being intoxicated depending on serum digoxin level and clinical manifestations: gastrointestinal symptoms (GI), bradycardia or atrioventricular block (Brady) or electrocardiographic signs of automaticity (Auto), as in Table 2.

Gideon Koren,[1] *M.D. and Stuart M. MacLeod,*[2] *M.D., Ph.D.*

Postmortem Redistribution of Digoxin in Rats

REFERENCE: Koren, G. and MacLeod, S. M., "Postmortem Redistribution of Digoxin in Rats," *Journal of Forensic Sciences*, JFSCA, Vol. 30, No. 1, Jan. 1985, pp. 92–96.

ABSTRACT: Adult male Wistar rats were treated with either 0.1 or 3 mg/kg body weight · day of digoxin for five days, then killed and stored at 4°C for 12 h in an attempt to mimic the normal preautopsy procedures in our hospital. In rats treated with 0.1 mg/kg body weight · day, the antemortem serum digoxin concentrations (SDC) were 1.1 ± 0.4 ng/mL while the 12-h postmortem concentration was markedly increased (16.3 ± 5.9 ng/mL) ($P < 0.01$). In rats treated with 3 mg/kg body weight · day, SDC was not changed significantly (11.2 ± 4.8 ng/mL antemortem and 13.3 ± 6 ng/mL postmortem). Postmortem redistribution of digoxin was assessed by injection of ^{125}I-labelled digoxin with or without pretreatment with the unlabelled drug. The results indicate that after death passive redistribution of digoxin may take place. When the SDC are within the therapeutic or low toxic range, digoxin may reenter the blood. High antemortem serum concentrations of digoxin may prevent such passive redistribution. Therefore, antemortem digoxin intoxication cannot be reliably inferred on the basis of high postmortem levels of the drug. Digoxin intoxication can be ruled out when postmortem SDC remain within the therapeutic range. The above changes cast doubt on some of the forensic and cardiologic literature, which has in the past been based on incorrect assumptions concerning postmortem behavior of digoxin.

KEYWORDS: pathology and biology, digoxin, blood, postmortem examinations, pharmacokinetics, redistribution

Digitalis intoxication is a serious clinical emergency that, in adults, has been reported to be associated with digoxin serum concentrations higher than 2.5 ng/mL [*1*]. Since the drug is frequently administered to critically ill patients, the possibility of digitalis intoxication must be considered in every unexplained death of a digitalized patient [*2*]. Recently, several studies have reported postmortem serum digoxin concentrations significantly higher than those normally measured during life [*3–5*]. Holt [*6*] and Doherty [*7*] have suggested that after death a new equilibrium between the blood and tissues is established, resulting in a higher digoxin concentration in the blood. However, no controlled experiment has been reported to prove this assumption.

The phenomenon does create difficulties in interpretation of postmortem serum digoxin levels in cases where antemortem serum levels are not available. Moreover, studies in which postmortem tissue versus plasma concentrations of digoxin have been assessed are further confounded since it is possible that these values may not reflect the normal distribution of the drug in life, but rather a new and radically altered distribution [*5,8–10*]. There are no studies of changing digoxin distribution in the terminal stages of either acute or chronic cardiac failure. The available data imply that substantial shifts in distribution may occur.

It was the aim of our studies to describe any discrepancies that may exist between antemortem and postmortem digoxin levels in the blood and in various tissues using both thera-

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peutic and toxic digoxin levels in a rat model. In the second stage of this experiment we studied possible postmortem redistribution of the drug using radiolabelled digoxin.

Materials and Methods

Antemortem and Postmortem Digoxin Serum Levels

Sixteen adult male Wistar rats were treated with either 0.1 (eight rats) or 3 mg/kg body weight (eight rats) of intramuscular digoxin per day for five days. These dose regimens were chosen because of the high LD_{50} of digoxin in the rat, which exceeds by far the human values [11] and the rapid elimination rate of the cardiac glycoside in rodents. On the sixth day they were killed by cervical dislocation and serum samples for measurement of digoxin levels were obtained immediately from the heart. Carcasses were then stored in a refrigerator at 4°C for 12 h, in an attempt to mimic the normal preautopsy procedures in our hospital. After this storage period samples for measurement of digoxin concentrations were again obtained from the heart. Digoxin serum levels were assessed by the routine radioimmunoassay (New England Nuclear Ltd.).

Postmortem Redistribution of Digoxin

Five adult male Wistar rats were injected intramuscularly with ^{125}I-labelled digoxin (New England Nuclear) 0.015 μCi with specific activity of 2000 dpm/pg. Two hours later they were killed by cervical dislocation and samples of cardiac muscle, diaphragm, liver, and kidney were removed. Renal cortical, liver, heart, and diaphragm radioactivity was measured in a γ counter (dpm per gram of wet tissue) and compared to the blood radioactivity (per gram of blood). The carcasses of these five rats were then stored as described above in a refrigerator at 4°C for 12 h, following which various tissue samples were again removed, radioactivity reassessed and compared to blood radioactivity.

In the above studies comparisons were made by the two-tailed student's *t* test for unpaired results.

In a further study of postmortem digoxin redistribution five adult male Wistar rats were treated for five days with unlabelled digoxin 1 mg/kg body weight. On the sixth day they were injected with ^{125}I-labelled digoxin 0.015 μCi, 2 h after the daily injection of the unlabelled drug. Two hours later they were killed and samples of cardiac muscle, diaphragm, liver, and kidney were removed. Renal cortical, liver, heart, and diaphragm radioactivity was measured (dpm per gram of wet tissue) and compared to blood radioactivity (per gram of blood). As in earlier experiments, the carcasses were subsequently maintained in a refrigerator at 4°C for 12 h, following which the radioactivity of the various tissues was compared to the serum reactivity.

Results are expressed throughout the text as mean ± standard deviation. Results from simultaneous studies were compared by the two-tailed student's *t* test for paired results.

Results

The mean digoxin concentration of serum obtained from heart of rats treated with digoxin dose of 0.1 mg/kg body weight was within the therapeutic range for humans (1.1 ± 0.4 ng/mL), while the mean 12-h postmortem concentration was markedly increased (16.3 ± 5.9 ng/mL) ($P < 0.01$).

In the group of rats treated with a high digoxin dosage (3 mg/kg body weight) the antemortem level of serum digoxin was within the toxic range for humans (11.2 ± 4.8 ng/mL). In this group the mean serum concentration although slightly increased did not change significantly 12 h after death (13.3 ± 6 ng/mL).

3-60

D-2

Tissue : Plasma Distribution

Animals Injected with Radiolabelled Digoxin—The tissue : blood distribution ratio of ^{125}I digoxin is shown in Table 1. The antemortem data indicate high tissue : blood ratio of digoxin in the kidney, liver, diaphragm, and cardiac muscle.

In the 12-h postmortem specimens, the concentration of the labelled digoxin in the blood was much higher than found in the antemortem samples (960 and 155 cpm/g, respectively, $P < 0.001$). Primarily because of this increase in blood digoxin concentration, tissue : blood ratios for labelled digoxin significantly decreased to approach unity in all tissues examined.

Previously Digitalized Animals Injected with Radiolabelled Digoxin—The tissue : blood distribution ratio of ^{125}I digoxin in animals given radioactive digoxin after earlier digitalization is shown in Table 2. The antemortem data demonstrate low tissue : blood ratios in the various tissues studied. These ratios are significantly lower than those observed in undigitalized rats receiving a single injection with radiolabelled digoxin ($P < 0.05$). Twelve hours later the tissue : blood ratio of labelled digoxin was found to be unchanged in the digitalized rats in all tissues tested.

Discussion

In common with earlier reported human studies [3–5], the first part of our experiment indicates that in the rat low antemortem serum levels during life tend to increase significantly after death. On the other hand, this phenomenon was not observed following exposure of test animals to higher digoxin dosage. In that situation the postmortem levels were similar to the higher antemortem concentrations. The combination of these two observations leads to the suggestion that passive redistribution of digoxin may occur after death. During life it appears that most of the drug is actively accumulated by cardiac and skeletal muscle as well as by kidney and liver [12]. The tissue : serum digoxin ratio during life is high above unity for these tissues, accounting for the large distribution volume of the drug [12]. Spiehler has found high concentration of digoxin in the brain of toxic cases and not of therapeutic

TABLE 1—*Antemortem and 12-h postmortem tissue : blood distribution ratio of ^{125}I digoxin in undigitalized rats injected with the radiolabelled digoxin 2 h before being killed.*

Ratio	Antemortem	12-h Postmortem	Significance of Change
Kidney : blood	7.9 ± 5.4	1.1 ± 0.5	$P < 0.05$
Liver : blood	8.8 ± 2.3	1.2 ± 0.3	$P < 0.01$
Cardiac : blood	10.6 ± 6.6	0.9 ± 0.2	$P < 0.05$
Diaphragm : blood	6.1 ± 1.3	0.8 ± 0.2	$P < 0.05$

TABLE 2—*Antemortem and 12-h postmortem tissue : blood distribution ratio of ^{125}I digoxin in rats exposed for five days to toxic doses of the drug.*

Ratio	Antemortem	12-h Postmortem	Significance of Change
Kidney : blood	2.4 ± 0.2	2.3 ± 0.3	N.S.[a]
Liver : blood	0.9 ± 0.2	0.9 ± 0.2	N.S.
Cardiac : blood	0.9 ± 0.2	0.9 ± 0.3	N.S.
Diaphragm : blood	1.0 ± 0.2	1.6 ± 0.6	N.S.

[a] N.S. = No significance.

3-61

D-3

cases, thus suggesting that digoxin content of the medulla may be useful in confirmation of antemortem blood digoxin concentrations [13]. After death, it appears that cessation of the active modulating accumulation process takes place, and, as a result, digoxin is redistributed passively from tissues containing digoxin in high concentration into areas of lower concentrations such as the blood. On the other hand, when serum concentrations of digoxin are extremely high because of acute intoxication the lack of a gradient may block redistribution.

To study empirically this hypothesis, we monitored postmortem digoxin redistribution using digoxin labelled with ^{125}I. We measured the tissue : blood ratios for various tissues at the time of death and 12 h later. Our results indicate that in undigitalized rats given an acute dose of digoxin, digoxin accumulates during life in the various tissues in concentrations much higher than the serum concentrations. These results are consistent with DiGregorio's observations on the tissue distribution of digoxin in the rat [12], as well as with human studies [5,8–10].

The tissue : blood concentration ratio for digoxin 12 h after death approaches unity, indicating that in the various tissues equilibrium of digoxin concentrations with blood concentrations has been achieved. This indicates that after death the drug tends to leave the cells and to enter the extracellular as well as the intravascular compartment.

Conversely, redistribution of digoxin was inhibited in animals previously exposed to pretreatment with toxic doses of the drug in nonlabelled form. The radiolabelled digoxin given after such pretreatment did not enter tissues in large quantities in these animals probably because of earlier saturation of digoxin binding sites by the excessive amounts of unlabelled digoxin. During the 12 h after death a redistribution of digoxin did not take place as a result of the relative balance between the organ : blood distribution already established in the digitalized animals.

Our findings have several implications for the interpretation of postmortem digoxin levels in serum as well as in various tissue.

1. After death, passive redistribution of digoxin may take place. When the serum concentrations are within the therapeutic or low toxic range it appears likely that digoxin will reenter the blood. High antemortem serum concentrations of digoxin may prevent such a passive redistribution.

2. Antemortem digoxin intoxication cannot be reliably inferred on the basis of high postmortem levels of the drug alone.

3. Digoxin intoxication can be ruled out when postmortem serum concentrations remain within the therapeutic range.

4. Since the redistribution of digoxin depends upon the time after death, and probably on other, as yet unknown factors, any extrapolation from postmortem data to the distribution of the drug in life may be tenuous. The changes reported above cast doubt on some of the cardiologic literature [10–11,14], which have reported postmortem tissue digoxin concentrations as if these values accurately represent the antemortem distribution of the drug.

There is a pressing need for better postmortem human studies of digoxin distribution for purposes of both medicolegal and clinical understanding.

Acknowledgment

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Isolated myocardial fibrosis as a cause of sudden cardiac death and its possible relation to myocarditis.

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Abstract

In performing medicolegal autopsies on sudden deaths, there occur a number of cases in which no cause of death can be found. In particular, no evidence of macroscopic cardiac abnormalities can be observed. However, extensive histological screening may reveal isolated areas of myocardial fibrosis. The five cases presented discuss the etiology of this fibrosis and its possible relation to myocarditis. The cases involve white women between the ages of 19 and 25 with no previous medical history. The weight of the heart in all five cases was normal. Macroscopic evidence of fibrosis was visible in four out of five cases. No other macroscopic abnormalities were observed. Histologically, there was evidence of scarring or interstitial fibrosis in all five cases. In four of the cases, additional screening permitted the observation of dispersed inflammatory foci consisting of lymphocytes, plasmocytes and macrophages. Two of the cases demonstrated eosinophil and neutrophil aggregates in the center of necrotic foci. No evidence of vascular inflammatory phenomena was observed in any of the five cases. According to the Dallas criteria, three of the five cases fulfill the requirements for myocarditis and one of the five cases for borderline myocarditis. The Dallas criteria, however, do not take into consideration the possible association between inflammation and myocardial fibrosis since many of the reported series of myocarditis have been from hospital autopsies or endomyocardial biopsies and have not taken into account sudden death from fibrotic sequelae of myocarditis.(ABSTRACT TRUNCATED AT 250 WORDS)

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3-64

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Differences in amiodarone, digoxin, flecainide and sotalol concentrations between antemortem serum and femoral postmortem blood.

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Abstract

1. The concentrations of amiodarone/desethylamiodarone, digoxin, flecainide and sotalol were measured in serum collected immediately prior to death and in postmortem blood collected from the femoral vein and artery of an 18-year-old male with congenital heart disease who developed a fatal arrhythmia. 2. The concentrations of all four drugs in the sample collected during life were consistent with the dosage given and in the range accepted for normal therapy. 3. There were no differences in amiodarone/desethylamiodarone, flecainide and sotalol concentrations in arterial or venous postmortem blood. 4. The concentrations of desethylamiodarone, digoxin, flecainide and sotalol but not amiodarone, were higher in postmortem blood than in antemortem serum. The flecainide concentration was significantly greater than the upper limit associated with toxicity in life. Without knowledge of the true concentration measured in life, this apparently high, toxic concentration would have suggested that death could have resulted from arrhythmogenic/proarrhythmic effects of the drug in excess. 5. These results further demonstrate the hazards in interpreting postmortem blood concentrations following suspected drug intoxication.

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3-65

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ARTICLE

Key Concepts in Postmortem Drug Redistribution

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Postmortem redistribution (PMR) refers to the changes that occur in drug concentrations after death. It involves the redistribution of drugs into blood from solid organs such as the lungs, liver, and myocardium. Drug properties such as volume of distribution, lipophilicity, and pKa are important factors. Basic, highly lipophilic drugs with a volume of distribution greater than 3 l/kg are most likely to undergo PMR. Examples include the tricyclic antidepressants, digoxin, and the amphetamines. The anatomical location of blood sampling can influence the drug concentration. The ideal site is a ligated or clamped femoral vein. Medical toxicologists participating in forensic cases involving drugs likely to undergo PMR must be aware of its potential contribution to the postmortem drug concentration. Correlation with laboratory data and any available antemortem or perimortem clinical information is necessary to render an appropriate opinion on the cause of death.

Keywords Postmortem changes; Forensic sciences; Cocaine; Antidepressants; Tricyclic; Pharmacokinetics

INTRODUCTION

Medical toxicologists are frequently asked to render a toxicologic probability statement in medicolegal cases where drugs may have been involved in the death of an individual. Part of the case evaluation involves review of forensic records, which often contain postmortem drug concentrations. Often no antemortem or perimortem drug blood is available for analysis, and clinical information about the deceased at the time of death may not exist if no medical attention was provided. While it is convenient to think of the human body as a static entity after death, this is clearly not the case. The concept of postmortem drug redistribution (PMR) must be taken into account when interpreting postmortem drug concentrations. Failure to recognize its importance can result in erroneous conclusions about cause of death. This article will serve as a review of postmortem drug redistribution, a discussion of the characteristics of the drugs most likely to undergo PMR, and the changes that occur in the body after death which influence its occurrence. Practical implications for the medical toxicologist are also discussed.

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HISTORY

Originally, research in the area of PMR focused on the barbiturates because of their frequent use, abuse, and involvement in fatalities. In 1960 it was discovered that a relationship existed between liver and peripheral (femoral vein) blood barbiturate concentrations and estimated time of death, with the liver concentrations being higher than peripheral blood (1). The relationship between the two became weaker after 5 h between death and drug sampling. Parker and colleagues (2) used a rat model with secobarbital to study the phenomenon of postmortem drug diffusion from the stomach. In a series of experiments, including postmortem intragastric introduction of secobarbital, they were able to determine that postmortem secobarbital levels in the liver increased up to 216 h after intragastric administration.

Subsequent work in the next two decades focused on the study of digoxin and the tricyclic antidepressants (TCA's). The postmortem behavior of digoxin was first investigated by Holt and Benstead (3) who found that in three patients suspected of having digoxin toxicity as their cause of death, blood samples from three different sites (right ventricle, femoral vein, neck veins) were significantly different, with femoral blood having a lower concentration than either of the other two sites. They therefore made the recommendation that postmortem blood should be collected from the leg veins for assessment of digoxin concentration.

One of the initial studies on TCA's and PMR was from Apple and Bandt (4) who demonstrated that postmortem liver concentrations of amitriptyline, desipramine, nortriptyline, and doxepin were well in excess of blood concentrations in

3-66

both TCA and non-TCA related deaths. This led them to speculate that postmortem release of drug might result in falsely elevated postmortem concentrations. Subsequently, the TCA's have become one of the best studied drug classes in PMR research.

As research into PMR continued into the present day, drugs of abuse such as morphine, cocaine, and methamphetamine have also been studied. Details on these drugs are discussed later in this review.

CELL DEATH

In order to fully understand why PMR occurs, an understanding of the changes that occur with cell death is necessary.

There are four key elements to the maintenance of cell structure and integrity. These include the maintenance of the integrity of cell membranes, aerobic respiration, synthesis of enzymatic and structural proteins, and preservation of the integrity of the genetic apparatus of the cell. With cell injury, a number of mechanisms occur which result in death of the cell and release of its contents, including xenobiotics. Aerobic respiration ceases, ATP production decreases, and anaerobic metabolism begins. Lactic acid and inorganic phosphates accumulate within the cell, causing a decrease in intracellular pH. The sodium-potassium ATPase pump then fails secondary to the decreased ATP production, with subsequent accumulation of sodium within the cell. Cellular edema then ensues, with dilation of the endoplasmic reticulum. Following this, the ribosomes detach from the endoplasmic reticulum, the mitochondrial matrix is destroyed, and the lysosomal membranes are injured with enzymatic leakage into the cytoplasm. The cell components are then progressively degraded with leakage of cellular contents into the extracellular space, and extracellular molecules then enter the remnants of the cell (5).

The time sequence for these events depends on the organ involved. Irreversible cell injury can be seen in the myocardium as early as 30 to 40 min after ischemia (5). In the liver, between 1 and 2 h of ischemia are required to produce irreparable damage, whereas brain neurons will show evidence of permanent injury after only 3 to 5 min (5).

FACTORS AFFECTING POSTMORTEM REDISTRIBUTION OF DRUGS

The reasons a drug may undergo PMR can be grouped into the properties of the drug and changes that occur in the body after death.

Drug Properties

Volume of Distribution

The volume of distribution (Vd) is defined as the amount of drug in the body divided by the plasma drug concentration, expressed in liters per kilogram (L/kg) of body weight. A number of factors affect Vd, including properties of the drug, age, gender, disease, and body composition (6). Drugs that are highly bound to plasma proteins but not to tissue components would be expected to have a small Vd equal to that of the plasma volume. Those drugs which distribute into muscle, adipose tissue, and other intracellular constituents will have a high Vd. Upon cell death and subsequent lysis, drugs are released into the plasma with a resultant increase in postmortem concentration. Drugs with a Vd greater than 3 L/kg have the greatest potential to undergo PMR (7).

Lipophilicity and pKa

Drug distribution is reliant on a number of factors, such as lipophilicity, pKa, energy-dependent transport, and tissue affinity of the drug. With respect to PMR, there are two important points. Firstly, lipophilic drugs and organic bases will concentrate in solid organs such as the lungs, liver, and myocardium. This provides a concentration gradient for passive diffusion after death. Secondly, the contents of a cell are largely aqueous and become acidic after death. Since a basic drug will be progressively more ionized in an increasingly acidic medium, after cell lysis occurs, basic drugs will distribute more readily as a result of being transported in the acidic fluid in which they are dissolved.

Changes That Occur in the Body After Death

Passive Diffusion from Solid Organs

The organs that are in close proximity to major blood vessels and heart and therefore most likely to play a role are the esophagus, stomach, pylorus, proximal duodenum, left lobe of the liver, and the lungs. Hilberg (8) demonstrated in rats whose trachea was ligated experimentally that amitriptyline could still be found in the left lobe of the liver 96 h after death compared with 1.5 h if the trachea was not ligated, suggesting that postmortem agonal aspiration may be a contributor to drug redistribution. This is important in interpretation of cardiac drug levels, which may be falsely elevated as a result of diffusion from surrounding organs.

Putrefaction

Body decomposition can also contribute to changes in drug concentrations after death. Robertson and Drummer studied the bioconversion of the nitrobenzodiazepines flunitrazepam, clonazepam, and nitrazepam in the presence of eight species of enteric bacteria which would be commonly found in the gastrointestinal tract after death. They determined that these drugs were metabolized by a number of bacteria, most rapidly by the facultative anaerobes *Clostridium perfringens* and *Bacillus fragilis* (9). The rate of metabolism was reduced when the reactions were allowed to occur at +4°C compared to temperatures ranging from 22 to 37°C, highlighting the importance of preservation of corpses at cool temperatures.

Ongoing Blood Movement

The position of the body after death and subsequent movement of the body by law enforcement and medical

3-67

TABLE 1
Factors which influence postmortem redistribution of drugs

Cell death
Putrefaction
Diffusion from stomach to nearby organs
Body position and movement after death
Drug characteristics (lipophilicity, pKa, Vd)

personnel may have an effect on PMR. One animal study demonstrated that liver secobarbital levels were significantly higher in rats placed in a "cranial end up" position compared to those in a "cranial end down" position (2). It is not clear how significant the contributions of these phenomena are to human cases of PMR.

Table 1 summarizes some of the influences on postmortem redistribution of drugs.

EXAMPLES OF DRUGS KNOWN TO UNDERGO PMR

While PMR has been studied for multiple drugs (10–15), there are a few drugs which, because of their frequent use and abuse, are discussed in greater detail. It is important to note that these data are largely from animal studies or case reports. Data from animal studies are not necessarily transferable to human cases, in part because the important anatomical structures in most animal models are closer to each other than the corresponding organs in humans. This makes diffusion of drugs potentially easier because of a shorter travel distance.

Tricyclic Antidepressants (TCAs)

The TCAs are perhaps the most extensively studied drug for the concept of PMR, even acting as the control group for comparison with other drugs (16). They exhibit a large volume of distribution, are basic, and highly lipophilic. Their ability to undergo PMR has been demonstrated both in studies where they have been determined to be the cause of death and where they were not thought to be a contributing factor (4,17,18). TCAs can redistribute from the lungs and concentrate in the left heart chambers via the pulmonary venous system (19). In addition, they can bind to the myocardium and can therefore be released into the left and right heart chambers (20,21).

Digoxin

Several studies have shown that digoxin is a drug which undergoes PMR from the myocardium, lungs, and liver (22,23). Vorpahl and Coe (24) studied antemortem and postmortem digoxin levels in 27 patients. Based upon the postmortem digoxin concentrations, they concluded that the diagnosis of digoxin toxicity would have been erroneously made in 89% of the patients, none of whom had accidentally or intentionally overdosed on digoxin. While femoral vein blood was not collected consistently in all patients, the femoral vein digoxin concentration was consistently lower than heart blood. This emphasizes the importance of peripheral over central blood sampling to decrease the contribution of PMR to the obtained drug concentration.

Morphine

Pharmacologically, one would expect morphine to undergo PMR as it has a Vd of 3–5 L/kg and is lipophilic at physiologic pH. Animal models have consistently shown that morphine does undergo redistribution. In separate studies, Koren (25) and Sawyer (26) demonstrated that cardiac blood samples taken from rats 24 and 96 h after death displayed significant increases in morphine concentration compared to the perimortem period.

Conflicting data exist in humans on the PMR of morphine. One group of investigators found that, in 40 heroin related deaths, there was no significant difference in concentrations between admission and autopsy blood samples, and while there was a trend for higher concentrations in heart blood compared to femoral or subclavian blood, the difference was not significant (27). However, others (28–31) have found that morphine does undergo PMR, finding obvious differences between central and peripheral concentrations of morphine, morphine-3-glucuronide, and morphine-6-glucuronide.

The explanation for the discrepancy between these studies is likely due to variation in sites chosen for sampling (e.g., using central sites only), and variation in the water content and hematocrit amongst patients. Blood samples with a low hematocrit and high water content will contain the highest morphine concentrations. One study demonstrated a range of 65 to 83% for water content and 25 to 75% for hematocrit for 10 blood samples from four patients suspected of heroin overdose (32). In addition, not all of the investigators obtained their femoral blood samples after first ligating the femoral vein. Since both morphine and heroin undergo hepatic metabolism, one would expect high concentrations of both morphine and its metabolites in inferior vena cava (IVC) blood. Without first ligating the femoral vein, IVC blood can potentially flow in a retrograde fashion to the iliac and femoral veins, falsely elevating true femoral vein morphine and metabolite concentrations. Finally, the time from death to blood sampling also varies depending upon when forensic teams make contact with the body. In one study this time ranged from 3–144 h postmortem (32).

In attempting to explain the discrepancy between animal and human studies on the PMR of morphine and its metabolites, Logan and Smirnow (32) have suggested that the type of animal model may partially account for the differences observed. They contend that in small animal models there is an increased risk of transfer of blood between the major vessels, and accelerated release of fluid from tissue to replace that blood used for sampling, resulting in falsely elevated morphine concentrations as a result of fluid shifts.

Caution is advised in extrapolating the results from animal studies to human cases.

Cocaine

Cocaine binds to the myocardium and can be released into the heart blood after death in concentrations greater than those found in the femoral vein, suggesting that it is likely to undergo PMR (20). However, its rapid metabolism (half-life 0.5–1.5 h) makes it difficult to detect postmortem. In vitro studies using unpreserved blood demonstrate that cocaine is quickly hydrolyzed by pseudocholinesterase and hepatic esterases to ecgonine methyl ester (EME), whereas chemical hydrolysis is responsible for its metabolism to benzoyl ecgonine (BE) (33,34). Both EME and BE have longer half-lives than the parent compound (3.5–6 and 5–8 h, respectively). Cocaine is also more likely to be metabolized in a warm, alkaline environment, which may explain its ongoing metabolism after death (34). Two techniques used by pathologists to prevent its metabolism are refrigeration of blood samples at 4°C and addition of sodium fluoride (34).

Several studies (35,36) have attempted to find predictable site and time-dependent differences in postmortem blood concentrations of cocaine and its metabolites and have been unsuccessful. The reasons for this include differences in handling of corpses and blood samples (refrigeration vs. room temperature), lack of consistent sites chosen for blood sampling, and possibly incomplete distribution of cocaine if death occurred rapidly after insufflation, inhalation, or intravenous injection. Some authors (37,38) have suggested that skeletal muscle and brain may be more appropriate tissues for postmortem cocaine analysis, in particular the brain because of its lipid rich environment. Whether brain sampling has become common practice amongst pathologists where cocaine toxicity is suspected is not clear.

Amphetamines

Amphetamines are also highly bound to the myocardium and have been shown to undergo PMR (39). Included in this category are methamphetamine (39–42), para-methoxyamphetamine (PMA) (43), 3,4-methylenedioxyamphetamine (MDA) (44), and 3,4-methylenedioxymethamphetamine (MDMA) (44–46).

The reader is referred to other references to find more comprehensive lists of drugs which probably do and do not undergo PMR (47).

PRACTICAL IMPLICATIONS FOR THE MEDICAL TOXICOLOGIST

The medical toxicologist must consider a number of factors in interpreting postmortem drug concentrations.

Sampling Location

Peripheral blood is less likely to be subject to the postmortem elevations in drug concentrations seen in central blood sources such as the heart (28,48). The femoral vein is the preferred site of sampling, with care taken to ligate or clamp the vein proximally prior to sampling to eliminate any contribution from the iliac vein or vena cava. The femoral vein is a logical site since a peripheral vein is where samples are most often collected for pharmacokinetic modeling and determination of concentration-effect relationships in living patients and volunteers. Heart blood is probably one of the least informative areas for sampling because the redistribution of drug from the lung, liver, or myocardium affects the resulting drug concentration, and should therefore not be used without a corresponding peripheral blood sample. Similarly, blind needling of the chest is not advised because it can result in a sample from any cardiac chamber or great vessel (49).

Alternatives to Blood

Other tissues such as the posterior aspect of the right lobe of the liver, skeletal muscle, lung apex, and vitreous humor may be used for measurement of postmortem drug levels. Of these, the vitreous, because of its isolation, appears to be less susceptible than blood to postmortem changes. It is also a more simple environment than putrefied blood, containing 98–99% water (50). Historically, vitreous drug concentrations have been difficult to measure because of the small volume of the sample and the variation in the ability of the laboratory instruments to measure a vitreous specimen (51). It has been shown to be useful for detection of cocaine (52), benzodiazepines (50), and methadone (53). It may also be a more ideal medium for measurement of postmortem drug concentrations if the body has undergone considerable bleeding, decomposition, or burning (54).

The ideal medium for detection of postmortem drug concentrations would be well protected from decomposition, closely approximate ante- or perimortem concentrations, and be reliable. Unfortunately, variables such as the time from death to sampling, decomposition, and position of the body may influence drug accumulation in a specific site. It may therefore be ideal to collect samples from several tissue sites and types, such as the left ventricle, ligated femoral vein, the posterior lobe of the right liver, and the vitreous.

Time of Sampling

The time that the autopsy and blood sampling were performed may not correspond to the drug concentration at the time of death. This has been demonstrated in a rat model using secobarbital. Autopsies were performed anywhere from immediately after death to 7 days after death. With increasing time between death and autopsy, secobarbital concentrations increased (55). As previously discussed, the variation in time from death to blood sampling may account for the differences between studies in concentrations of morphine and its glucuronide metabolites as well as the detection of cocaine and its metabolites.

3-69

Correlation with Antemortem Clinical Information

Ideally, all blood levels should be correlated with available clinical information at or around the time of death to determine if the deceased was exhibiting characteristic features of toxicity from the drug in question. For example, it would be helpful to know that a patient with an elevated peripheral blood postmortem methamphetamine concentration was also hypertensive, tachycardic, diaphoretic, and agitated when seen in the emergency department just prior to death.

Central to Peripheral Blood Ratio

Knowledge of the central to peripheral (C/P) blood ratio for a drug may provide helpful information about whether it may undergo PMR. In one study involving 320 cases where postmortem cardiac (central) and femoral (peripheral) blood was obtained, basic drugs with a large volume of distribution displayed the largest C/P ratios. The authors developed a list of such ratios for 113 drugs (56). Drugs with higher ratios are thought to have greater potential for PMR. Unfortunately, the C/P ratio did not correlate with whether postmortem peripheral blood drug concentrations were considered to be therapeutic, toxic, or fatal.

A variation of the C/P ratio is the postmortem/antemortem (P/A) drug ratio, which has been studied by Cook and colleagues (57). This ratio was developed for seven drugs based upon concentrations in antemortem and postmortem peripheral blood samples. While they determined that drugs with high postmortem C/P ratios also had high P/A ratios, the P/A ratio was found to be unreliable in estimating antemortem drug concentrations from postmortem measurements. They concluded that not only was PMR an important contributor to the differences between antemortem and postmortem concentrations, but also recommended greater standardization in the site of blood sampling, with a ligated femoral vein as their site of choice.

Other Biochemical Tests

The potential for biochemical tests to be used as markers for PMR has been investigated by Langford and Pounder (58). Their objective was to determine if biomarkers such as amino acids were able to indicate if redistribution had affected the drug concentration in a particular blood, fluid, or tissue sample. Seventeen amino acids, hepatic transaminases, and amitriptyline and nortriptyline drug concentrations were studied in blood, vitreous, bile, ascitic fluid, and muscle from a single human case of death secondary to amitriptyline toxicity. Hepatic transaminases had a poor correlation with drug concentrations in the inferior vena cava, suggesting that they were poor indicators of PMR from the liver. Amino acids, particularly methionine, did show a positive correlation with drug concentrations from the pulmonary vasculature, indicating that they may be useful markers for PMR from the lungs. To our knowledge, this has not become common practice in forensic pathology.

TABLE 2
Questions the medical toxicologist must ask when interpreting a postmortem drug concentration

1. What site was used for the blood sample?
2. If the femoral vein was used, was the vein ligated or clamped prior to sampling?
3. Was more than one site used for sampling?
4. Were tissues other than blood used for sampling (e.g., vitreous, lung, liver, skeletal muscle)?
5. How long after death was the sample taken?
6. How was the body stored in the interval between death and blood sampling?
7. Is there evidence of significant decomposition in the body?
8. Under what conditions was the blood sample collected and stored?
9. How long was the delay between when the sample was collected and when it was analyzed?
10. Is there any antemortem or perimortem clinical information available on the deceased?
11. Is there any antemortem or perimortem blood available for analysis?
12. What are the properties of the drug involved (pKa, lipophilicity, Vd)?

Drug Blood Level Tables

Several tables and textbooks with therapeutic, toxic and lethal drug blood values are available and can serve as a helpful guide (59–61). However, their authors admit that PMR is not always taken into account in developing these tables. Tables which are based upon larger samples of patients and which include postmortem femoral blood levels may be more reliable (62). Some include recommendations on correction factors to calculate expected levels for infants and children (59).

Table 2 contains important questions the medical toxicologist should ask when interpreting a postmortem drug level.

CONCLUSION

Postmortem drug redistribution refers to the changes that occur in drug distribution after death. It involves not only distribution from solid organs such as the lungs and liver, but also diffusion from organs such as the stomach to nearby organs such as the heart and the left lobe of the liver. Factors such as volume of distribution, lipophilicity of the drug, pKa, and time and site of drug sampling are all important. Medical toxicologists must be aware of this phenomenon when interpreting drug concentrations in forensic cases. Knowledge of site of blood sampling, perimortem clinical information, and characteristics of the drug will aid the medical toxicologist in rendering a more accurate probability statement about the contribution of drugs to a person's death. Further study of the

optimal site and method of sampling, the ideal medium (blood vs. vitreous), and the use of other biomarkers as indicators of postmortem drug redistribution is needed.

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3-72

CLINICAL REVIEW

Editor: Stephen C. Hammill, M.D.

Implications of Obstructive Sleep Apnea for Atrial Fibrillation and Sudden Cardiac Death

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Obstructive Sleep Apnea. Obstructive sleep apnea (OSA) is a sleep-related breathing disorder with important cardiovascular consequences, including arrhythmogenesis. The unique pathophysiology of OSA results in multiple intermediate mechanisms that may promote atrial fibrillation, ventricular arrhythmias, and sudden cardiac death. These mechanisms may act acutely to trigger nocturnal dysrhythmias, or chronically by affecting the electrical and myocardial substrates. Burgeoning epidemiological data have identified an increased risk for atrial fibrillation and sudden cardiac death related to OSA. Currently, few data exist to support the efficacy of OSA therapy, namely continuous positive airway pressure, as an adjunct for arrhythmia prevention or management. *(J Cardiovasc Electrophysiol, Vol. 19, pp. 997-1003, September 2008)*

arrhythmia, atrial fibrillation, sleep, sleep apnea, sudden cardiac death

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder with pulmonary, neurological, metabolic, and cardiovascular consequences. Important pathophysiological and epidemiological relationships have been identified between OSA and clinically significant arrhythmias, including atrial fibrillation (AF) and sudden cardiac death (SCD). In this review, we will provide an introduction to OSA that is relevant to heart rhythm specialists, describe the potential pathophysiological mechanisms linking OSA to AF and SCD, and discuss the available epidemiological data regarding the relationship between OSA and important arrhythmic outcomes.

Obstructive Sleep Apnea

Pathophysiology and Definitions

OSA is characterized by multiple transient episodes of pharyngeal obstruction that result in repeated interruptions of airflow (apneas and hypopneas) during sleep. The principal mechanisms relate to structural and functional abnormalities in pharyngeal soft tissue and muscle, as well as altered neural and ventilatory feedback loops.[1] Chemoreceptor activation by hypoxemia and hypercapnia during apnea results in hyperventilation and transient awakening, which is usually subconscious but electroencephalographically confirmed. Sleeping supine promotes airway collapse due to posterior displacement of the mandible, soft palate, and tongue. For similar reasons, micrognathia, retrognathia, tonsillar hypertrophy, macroglossia, and acromegaly increase the risk for OSA.

An obstructive apnea is an absence of airflow for 10 or more seconds with concomitant chest and abdominal wall movement representing active ventilatory efforts. An obstructive hypopnea is defined as a 50% or more decrease in airflow for at least 10 seconds associated with a more than 4% decrease in oxygen saturation and the typical chest and abdominal wall movements. The severity of OSA is most commonly described by the average number of apneas and hypopneas per hour of sleep, the apnea–hypopnea index (AHI). The AHI ranges from zero to the hundreds. An AHI of five or more is used to diagnose OSA; however, that threshold is arbitrary and even an AHI less than five has a direct relationship with important clinical consequences of OSA, including cardiovascular disease.[2] Other measures of OSA severity include the magnitude of nocturnal oxygen desaturations, quantitated by the mean or lowest oxygen saturations and the cumulative time during sleep with an oxygen saturation less than 90%. Sleep efficiency (the proportion of time in bed that is spent sleeping) is another important metric of the severity of the sleep disorder, since independently of its cause sleep deprivation is associated with cardiovascular disease.

Clinical Presentation

The most common symptom of OSA is excessive daytime sleepiness that interferes with usual activities such as conversing, eating, reading, or driving. Anther symptom distinct from this is sleepiness immediately on waking. "Symptoms" usually reported by a bed partner are snoring (ubiquitous) and

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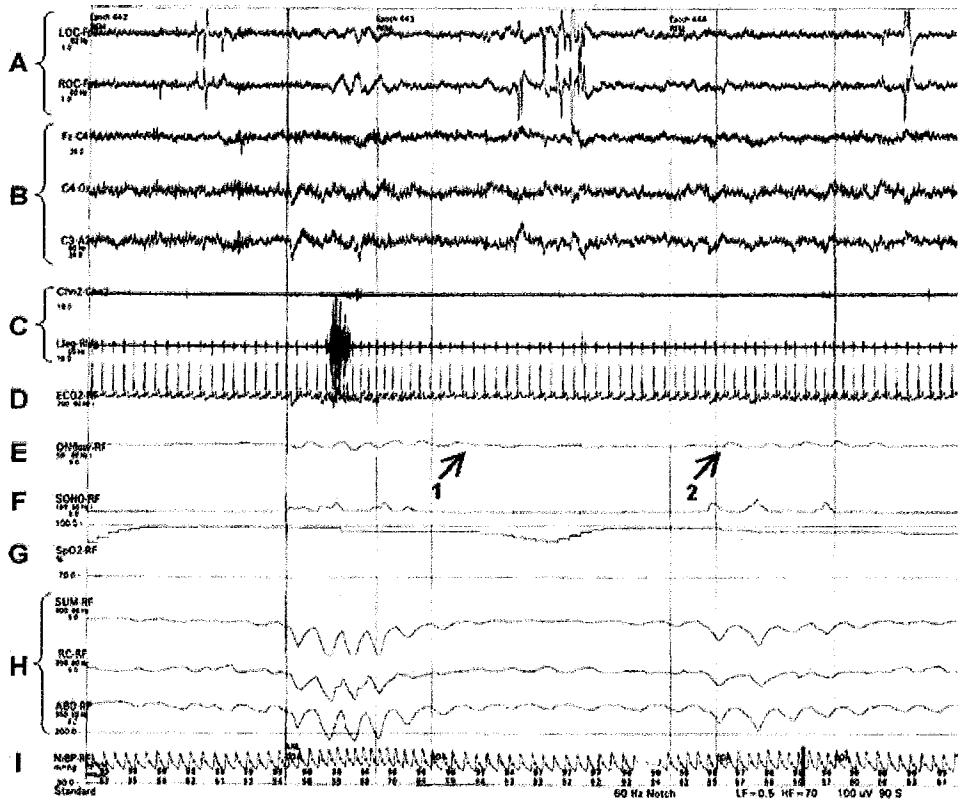

Figure 1. *Polysomnography. The tracing shows the electrooculogram (A), electroencephalogram (B), electromyogram (C), electrocardiogram (D), measures of airflow (E), sonogram (F), oximetry (G), measures of thoracoabdominal movements (H), and blood pressure (I) during 90 seconds of REM sleep in an individual with obstructive sleep apnea. Arrow 1 identifies initiation of an obstructive apnea. During this apnea, airflow (E) and snoring (F) are absent, and oxygen saturation decreases (G). The paradoxical movements of the chest and abdomen (H) during the apnea reflect futile ventilatory efforts and mark this apnea as an obstructive apnea rather than a central apnea. Arrow 2 identifies the end of the obstructive apnea, at which time the heart rate accelerates (D), airflow (E) and snoring (F) resume, and chest and abdominal movements become synchronous and effective (H). Reproduced with permission from Gami AS, Caples SM, Somers VK: Obesity and obstructive sleep apnea. Endocrinol Metab Clin North Am 2003;32:869.*

witnessed apneas (an important sign due to its specificity). Other symptoms include morning headaches, dry mouth, sore throat, gastroesophageal reflux, and nocturia. Severe OSA may cause cognitive difficulties, including problems with memory, mood, and behavior.[1]

Most people with OSA are overweight or obese. However, since nearly one-third of people with OSA are not obese, normal weight does not exclude the diagnosis.[3] Other morphologic features, such as increased neck circumference, narrow oropharynx, large uvula, and retrognathia, are more specific than body mass index for OSA.

Diagnosis of OSA

Despite the fact that age, obesity, neck circumference, snoring, and witnessed apneas are typical characteristics of OSA, one-half of experts' diagnoses are inaccurate when based purely on these historical and physical data. Screening tools perform slightly better. The Epworth Sleepiness Scale, a questionnaire that systematically characterizes one's degree of sleepiness, correlates well with OSA severity. The Berlin Questionnaire predicts OSA by incorporating body mass index, hypertension status, and characterization of snoring and daytime sleepiness. It has been validated in general medicine and cardiovascular disease patients but not in community populations.

Laboratory-based testing includes overnight pulse oximetry and polysomnography (sleep study). Overnight oximetry is attractive due to its simplicity and ease of use in hospitalized or ambulatory patients. However, there are several limitations to its use and more research is necessary to identify its appropriate role in screening and diagnosis of OSA.

Polysomnography is the gold standard test for the diagnosis of OSA and other sleep-disordered breathing syndromes (Fig. 1).[1] Sleep is fully characterized by the continuous measurements of the electroencephalogram, oculogram, submental and tibial electromyograms, nasal and oral airflow, chest and abdominal wall motions, oxygen saturation, and often the electrocardiogram. These data allow for interpretation of sleep efficiency, sleep architecture, apnea and hypopneas, arousals, oxygen saturation, and cardiac rhythm. Because of the cost and difficulty of accessing laboratory-based polysomnography, portable sleep monitoring devices have been developed. Their accuracy and role in clinical practice are still being established.

Epidemiology

Population-based studies estimate that 20% of middle-aged, overweight but not obese, Western adults have OSA.[4] Partly due to the fact that only a quarter of these individuals have symptoms of OSA, a large proportion of people with OSA (up to 60%) remain undiagnosed. OSA is present in over

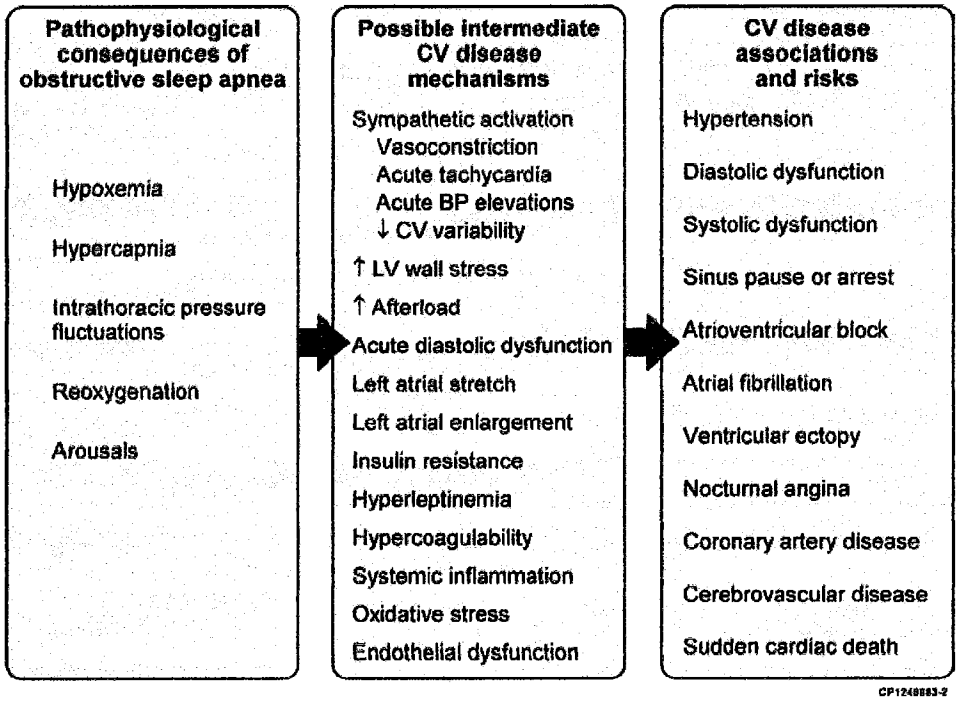

Figure 2. *Mechanisms of cardiovascular disease and arrhythmias in obstructive sleep apnea. The acute pathophysiological events of obstructive sleep apnea (left panel) may elicit multiple intermediate cardiovascular disease mechanisms (middle panel), which may promote the development of several cardiovascular conditions, including arrhythmias (right panel). Reproduced with permission from Gami AS, Somers VK: Sleep disorders and cardiovascular disease. In: Libby P, Bonow RO, Mann DL, Zipes DP, eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 8th ed. Philadelphia: Saunders, 2007.*

40% of individuals with a body mass index of 30 or more, and it is prevalent in patients with the metabolic syndrome.[3] Patients with established cardiac and vascular disease have a high prevalence of OSA: 50% of patients with hypertension, 50% of patients with atrial fibrillation requiring cardioversion, 33% of patients with lone atrial fibrillation, 33% of patients with coronary artery disease, 50% of patients with acute stroke, and 10–33% of patients with heart failure.[2] The chronic disease associations and acute pathophysiological mechanisms that may be responsible for these strong relationships are discussed later.

Mechanisms of Arrhythmias in OSA

Chronic Disease Associations

The risk of AF and SCD in individuals with OSA is influenced by its associations with obesity, hypertension, systolic and diastolic ventricular dysfunction, and cardiac and cerebral ischemic events (Fig. 2).[2] The AHI correlates directly with the development of incident hypertension, even when the AHI is in the normal range (less than 5). As a result, OSA is identified as a secondary cause of hypertension, which has implications for preventing or treating the downstream arrhythmic consequences of hypertension and left ventricular hypertrophy.

Similarly, left ventricular function is directly affected by OSA. Continuous positive airway pressure (CPAP), the principal therapy for OSA, improves left ventricular systolic function. An average 8% absolute percentage increase in ejection fraction has been demonstrated with the acute application of CPAP and after 1 month of chronic therapy.[5] The detrimental effects of OSA on left ventricular function may contribute to humoral and cellular changes that increase the risk for AF and SCD.

The risk of myocardial infarction is increased in patients with OSA,[2] which increases the risk of SCD due to the immediate dysrhythmic complications of acute coronary syndromes, as well as ventricular arrhythmias due to chronic ventricular remodeling and myocardial scar. Also, the risk of stroke is increased in patients with OSA.[2] This may be an important consideration when performing risk stratification and choosing stroke prophylaxis options in people with OSA and AF.

Hypoxemia

Apneic sleep is marked by cyclical episodes of hypoxemia, sometimes numbering hundreds per hour. Repetitive oxidative stress may be responsible for myocardial remodeling that promotes AF or the substrate for SCD. Severe hypoxemic episodes cause ventricular ectopy, which may lead to complex ventricular arrhythmias or SCD. The hypoxemia also leads, via activation of the chemoreflex and autonomic changes discussed later, to tachycardia and surges in blood pressure, particularly at the end of apneas. This increases myocardial oxygen demand at the same time that myocardial oxygen supply is at its lowest due to hypoxemia. This may result in myocardial ischemia during sleep, whether manifest as silent ST-segment changes or nocturnal angina.[2] These repetitive ischemic insults may cause acute hemodynamic stresses, promote ventricular fibrosis, or initiate ventricular dysrhythmias and SCD during sleep.

Autonomic Nervous System

In individuals with OSA, significant oscillations in both sympathetic and parasympathetic activity occur based on the progression of sleep stages and cycles of apneas and arousals.[6] In addition to its effects described earlier, hypoxemia, together with hypercapnia, activate the central and peripheral chemoreflexes during apneic sleep. This causes neural and humoral sympathetic activation, with demonstrable augmentation of peripheral sympathetic nerve activity, vasoconstriction, and increased serum catecholamine concentrations.[6] OSA also causes pronounced increases in parasympathetic tone. Apnea and hypoxemia activate the physiologic diving reflex, which results in profound parasympathetic tone due to the loss of the vagolytic effects of chest wall expansion during hypoxemic activation of the carotid bodies.[7]

While the complex relationship between the autonomic nervous system and AF is still being elucidated, it appears both sympathetic and parasympathetic mechanisms may initiate or maintain AF in susceptible individuals.[8] In OSA, relevant mechanisms may include the activation of atrial catecholamine-sensitive ion channels or the effects of vagotonia on atrial conduction properties. In addition to their acute autonomic fluctuations during sleep, individuals with OSA have chronically elevated sympathetic drive even during the awake state.[6] This may have important implications for the initiation and maintenance of atrial tachyarrhythmias, and for difficulty or failure of rate-control strategies in managing AF. Chronically elevated sympathetic activity is also associated with an increased risk of SCD.[9] OSA is associated with decreased heart rate variability, likely as a result of abnormal coupling of cardiac and ventilatory parasympathetic central nervous system inputs. Ventricular arrhythmias and SCD may be favored by abnormalities of ventricular repolarization, as evidenced by prolonged QT_c intervals and QT_c interval dispersion in individuals with OSA. The magnitude of these repolarization abnormalities are directly associated with the severity of OSA, reflected by both the AHI and the duration of nocturnal hypoxemia.[10]

Intrathoracic Pressure Changes

Repetitive and large fluctuations in intrathoracic pressures result from inspiratory efforts during obstructive apneas, and they can cause acute changes in cardiac hemodynamics and structure.[2] In healthy individuals, intrathoracic pressure during inspiration is normally about –8 cm H_2O. In patients with OSA, inspiratory efforts during obstructive apneas can generate intrathoracic pressures of less than –30 cm H_2O. This increases venous return to the right heart, decreases left ventricular compliance, and increases cardiac wall stress.[11,12] These processes also may cause stretching of the atria, which could possibly lead to left atrial enlargement (discussed later) and electrical remodeling at anchoring regions such as near pulmonary vein ostia. Evidence supporting these atrial effects include increased serum atrial natriuretic peptide concentrations and the common symptom of nocturia in individuals with OSA.[2] Activation of atrial stretch-sensitive ion channels by these mechanisms may have implications for the initiation of AF.

Left Atrial Enlargement

Enlargement of the left atrium may act as an intermediate mechanism conferring risk for AF due to OSA. Concomitant obesity, via larger body mass and increased total blood volume, and hypertension both play significant roles in left atrial enlargement in these individuals. Independent of these comorbidities, OSA is also associated with diastolic dysfunction. In people with OSA who are otherwise healthy, minor diastolic abnormalities are evident and correlate with the degree of hypoxemia in OSA.[2] Notably, OSA may increase left atrial size independently of obesity, hypertension, and diastolic dysfunction. A careful study of healthy, middle-aged adults found that left atrial volume indices, while still within the normal range, were larger in people with OSA.[13] OSA is independently associated with increased levels of inflammatory markers, including serum amyloid A and C-reactive protein, which may promote atrial remodeling and risk for AF.

Vascular Thrombosis

Multiple mechanisms in OSA promote arterial thrombosis, which has important implications for the risk of SCD and the cerebrovascular complications of AF. OSA is associated with increased platelet activation and aggregation, increased fibrinogen levels and decreased fibrinolytic activity during the night.[2] This is in contrast to the diurnal pattern of coagulation in normal individuals, in whom thrombosis is more likely during the morning hours. These may be important mediators of SCD, either due to myocardial infarction and stroke directly or to their dysrhythmic complications. Also, the risk of stroke in the setting of AF may be augmented in people with comorbid OSA.

OSA and Atrial Fibrillation

As early as 1983, a relationship between OSA and AF emerged from an observational study of 400 adults with moderate-severe OSA who underwent ambulatory electrocardiographic monitoring.[14] Nocturnal paroxysms of AF were recorded in 3% of these patients, and all patients who received definitive treatment of OSA had complete resolution of AF up to 6 months later. Further insights into this relationship were provided in 1998, when two controlled studies with very similar findings revealed a strong association between AF and sleep apnea in patients with moderate heart failure (average ejection fraction about 36%).[15,16] The prevalence of AF was about 20% in those with sleep apnea, and the relative risk of AF increased fourfold in its presence.

More recently, prospective studies have confirmed a high prevalence of sleep apnea in patients with AF, as well as an independent association between the two conditions. Continuous electrocardiographic monitoring in 566 people undergoing polysomnography found that AF occurred in 5% of those with severe sleep apnea and only 1% of those without sleep apnea.[17] These findings were similar to previous work described earlier,[14] but were strengthened by a control group. In a group of patients with lone AF (absence of any chronic or acute risk factors), the prevalence of polysomnogram-confirmed moderate sleep apnea (AHI more than 15) was reported as 32%.[18] While already strikingly high, an even higher prevalence of sleep apnea would have been identified in this otherwise healthy AF population if the standard

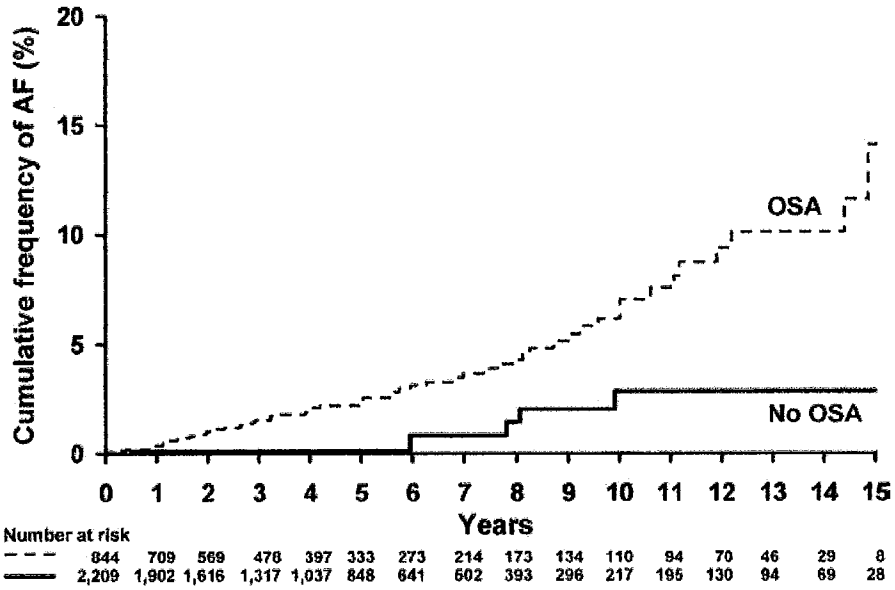

Figure 3. *Risk of atrial fibrillation in obstructive sleep apnea. The cumulative frequency of new-onset atrial fibrillation in 3,542 adults <65 years old, followed for an average 4.6 years after diagnostic polysomnography. Individuals with OSA are shown with the dashed line, and individuals without OSA are shown by the full line. AF = atrial fibrillation; OSA = obstructive sleep apnea. Reproduced with permission from Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, Somers VK: Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. J Am Coll Cardiol 2007;49:565.*

criterion (AHI of 5) was applied. In another study, the prevalence of OSA was compared between 151 consecutive patients undergoing electrical cardioversion of AF and 463 consecutive patients without AF being evaluated in a general cardiology practice.[19] Both groups had similar age, sex, body mass index, and prevalence of hypertension and heart failure; however, the patients with AF had a significantly higher risk of OSA (49% vs 33%), and multivariate analysis demonstrated a strong independent association between OSA and AF (odds ratio 2.2).

Beyond the cross-sectional data above, several longitudinal studies have shown that OSA predicts the occurrence of future AF. Two studies identified the role of OSA in recurrent AF. The first, a prospective study of 106 patients undergoing electrical cardioversion of AF, found that untreated OSA was associated with a remarkably high rate of AF recurrence at 1 year (83%), compared with patients with unknown OSA status (53%).[20] Both the lowest nocturnal oxygen saturation and the duration of sleep with oxygen saturations less than 90% independently predicted the recurrence of AF in these patients. A second study of 424 patients undergoing radiofrequency ablation of AF found that recurrence of pulmonary vein conduction during the initial procedure was predicted by OSA (RR 2.16).[21] The reason for this early recurrence may be related to the effects of OSA on left atrial electrical remodeling, fibrosis, and chamber enlargement.

Additional studies have assessed the occurrence of new-onset, or incident, AF in different patient populations. The first of these studies focused on patients at high risk for AF, those undergoing coronary artery bypass surgery, and found that sleep apnea predicted postoperative AF requiring therapy prior to hospital discharge.[22] An AHI of five or more predicted a 32% incidence of AF, compared with 18% in the control group, and the severity of oxygen desaturation predicted AF independently of other factors. In another study of 3542 patients without a history of AF who were undergoing their first sleep study, OSA and its severity predicted incident AF over an average of 5 years (Fig. 3).[23] In the nonelderly, incident AF was independently predicted by its usual clinical predictors, in addition to the magnitude of nocturnal oxygen desaturation (adjusted HR 3.29). The study also demonstrated that obesity and OSA both increased the risk for AF independently of each other. It is notable that in nearly all the studies above, oxygen saturation parameters were independently predictive of AF, which suggests that hypoxemia is an important pathophysiological mechanism linking OSA and AF.

OSA and Sudden Cardiac Death

While anecdote and personal experiences may have suggested a relationship between OSA and SCD, particularly nocturnal SCD, only recently have systematic data supported such a relationship. As discussed earlier, ventricular ectopy occurs in direct association with the hypoxemia of OSA. A large controlled study showed that over 25% of patients with severe sleep apnea have complex ventricular ectopy and that over 5% experience nonsustained ventricular tachycardia during sleep.[17] Independent of related comorbidities, sleep apnea was associated with over three times the risk of nonsustained ventricular tachycardia.

Two studies thus far have assessed SCD outcomes in people with OSA. The first compared long-term cardiovascular mortality in 107 patients with OSA stratified by CPAP use.[24] After an average of 7 years, SCD occurred in no patients who were compliant with CPAP, compared with 7% of noncompliant patients. Further establishing this relationship are findings from studies identifying a nocturnal preponderance of SCD in people with OSA (Fig. 4).[25] In 112 patients who had OSA confirmed or excluded by polysomnography and then had fatal SCD, those with OSA were more likely to die between 12 AM and 6 AM (RR 2.57). Those without OSA were more likely to die between 6 AM and 12 PM, which is consistent with the usual diurnal peak of SCD in the general population. Strikingly, about half of all SCD in patients with OSA occurred during the night. There was a direct relationship between the severity of OSA, as reflected by the AHI, and the risk of SCD during the night.[25]

Together, these data suggest that OSA is associated with an increased risk of SCD, particularly at night. However, additional research is necessary to confirm these findings and clarify the specific role of OSA beyond its comorbidities, the

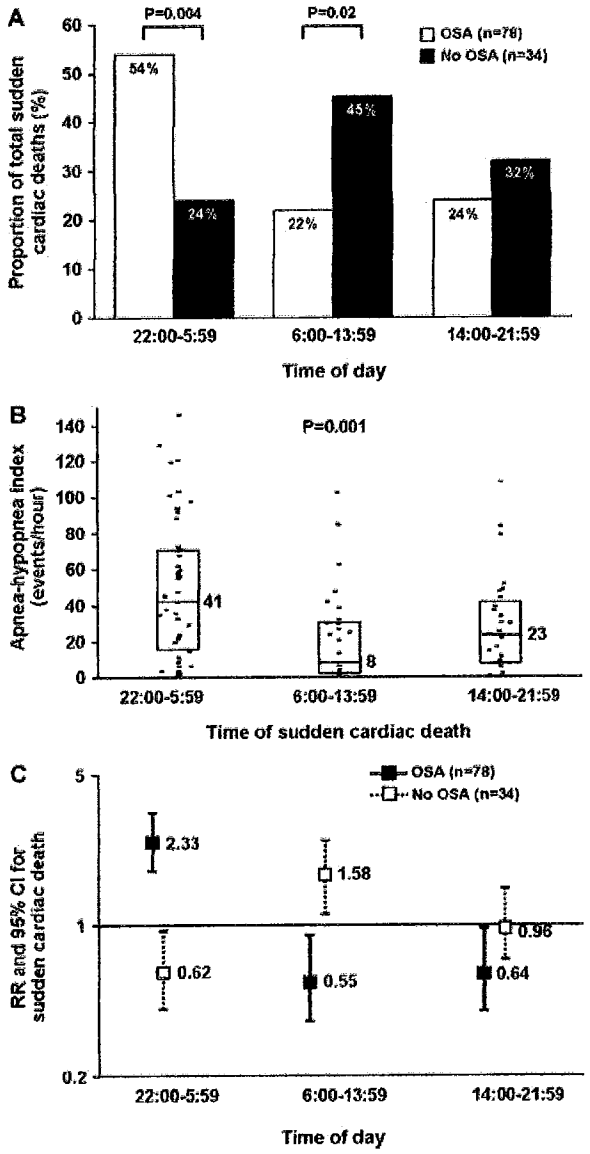

Figure 4. *Risk of nocturnal sudden cardiac death in obstructive sleep apnea. (A) Day-night pattern of SCD based on usual sleep-wake cycles. (B) The apnea–hypopnea index for individuals with SCD during 8-hour intervals of the day. The line within each box represents the median apnea hypopnea index, and the box represents the interquartile range (25th percentile to 75th percentile). (C) The RR of SCD during 8-hour intervals of the day, compared with the remaining 16 hours of the day, for individuals with and without OSA. The point and lines represent the RR and 95% confidence interval (CI). OSA = obstructive sleep apnea; RR = relative risk; SCD = sudden cardiac death. Reproduced with permission from Gami AS, Howard DE, Olson EJ, Somers VK: Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med 2005;352:1206.*

relevant pathophysiological mechanisms, and the potential benefit of OSA therapy for preventing SCD in appropriate patients.

OSA Therapy and Arrhythmia Outcomes

The principle therapy for OSA is CPAP. Compliance with CPAP is limited by side effects, such as rhinitis, nose bleeds, facial abrasions, and poor fit. These obstacles can usually be overcome by using alternative devices or adjuncts, such as humidified air, better fitting masks, and autotitrating or bi-level CPAP machines. Oral appliances, available in many designs, are an additional device therapy for OSA. They function by advancing the mandible, which increases oropharyngeal dimensions and reduces its collapsibility. Oral appliances improve OSA and quality of life, but they are less successful at doing so than CPAP; importantly, patients are more compliant with oral appliances than with CPAP. Surgical therapies for OSA include uvulopalatopharyngoplasty, for which few controlled studies exist, and tracheostomy, which is curative but reserved for debilitating or life-threatening situations. While weight loss, whether surgical or via lifestyle modification, is very effective in improving or curing OSA, the benefit lasts only as long as the weight loss itself. There are no effective drug therapies for OSA.

Effective CPAP therapy ameliorates many of the mechanisms that link OSA to arrhythmias.[25] Since apneas are abolished, hypoxemia is resolved. Nocturnal and daytime sympathetic activity decrease. Nocturnal blood pressure decreases, and hypertension management is improved. Nocturnal myocardial ischemia and angina are relieved. Left ventricular ejection fraction increases acutely and with chronic CPAP use. Furthermore, observational data suggest that the rate of myocardial infarction, stroke, and death is decreased by CPAP, although randomized controlled trials are necessary to confirm this.[25]

Only a few observational studies have assessed the effect of OSA therapy on arrhythmia outcomes. Cure of OSA by tracheostomy was shown to abolish nocturnal AF in 12 patients with severe OSA and nocturnal paroxysms of AF,[14] and a decrease in arrhythmias was noted after bariatric surgery in morbidly obese patients with OSA. The recurrence of AF 1 year after electrical cardioversion was compared between patients with treated and untreated OSA.[20] Maintenance of sinus rhythm was strongly associated with CPAP use, and only 42% of the treated patients had recurrent AF, compared with 82% of untreated patients.

CPAP reduces the frequency of ventricular arrhythmias in heart failure patients, a benefit likely mediated by amelioration of significant hypoxemia, decrease in sympathetic activity, and improvement in ventricular function. Observational longitudinal data demonstrate improved survival and prevention of cardiovascular events in OSA patients who use CPAP. The one study described earlier, showing a 7% rate of SCD in untreated patients and no SCD in treated patients, suggests that the benefits of CPAP may extend to SCD outcomes.

Currently, CPAP therapy is reimbursed by the Centers for Medicare and Medicaid Services for patients in whom surgery is a likely alternative therapy and who have at least moderate OSA (AHI 15 or more) or mild OSA (AHI 5–14) associated with OSA symptoms, hypertension, ischemic heart disease, or stroke. Because of the high prevalence of OSA in patients with cardiovascular diseases, the application of CPAP to all patients with OSA is likely impractical due to difficulties and costs of accessing polysomnography. Also, its benefits should not be assumed. A concerning study showed that CPAP therapy worsened cardiac function in heart failure patients with AF, compared with those with normal rhythm.[26] The role of OSA therapy in preventing arrhythmias in people with heart disease, and its potential as an adjunct to conventional antiarrhythmic therapies, remains to be proven in randomized controlled trials.

Conclusions

While AF and SCD remain the most clinically important arrhythmia syndromes, much uncertainty exists regarding their pathophysiology and risk factors. The current data support an important role of OSA in both AF and SCD, possibly acting via neural, humoral, hemodynamic, and metabolic mechanisms. Future research is required, first, to identify patient subgroups in which OSA imparts a heightened risk of arrhythmic outcomes; and second, to evaluate the role of OSA therapy in modulating such risk. At present, clinicians caring for individuals with cardiovascular disease should recognize the high prevalence of comorbid OSA and its clinical manifestations, and high-risk patients should be referred for polysomnography in order to improve their quality of life and possibly prevent or manage clinically significant arrhythmias.

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